Traditional and Non-traditional Cardiovascular Risk Factors in the Chronic Dialysis Population at Chris Hani Baragwanath Academic Hospital and Sebokeng Provincial Hospital

Dr Jose Jacob

Student number: 0701877

Department of Internal Medicine, Faculty of Health Sciences,

University of the Witwatersrand, Johannesburg, South Africa

E-mail address: joson88@gmail.com Cell: +27 837980080

ORCiD: 0009-0004-0029-355X

A Research report (in the format of a "submissible" publication to WJCM) submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirements for the degree of Master in Medicine

Johannesburg.

Co-authors and Supervisors:

Dr Gloria Teckie – BSc, BSc(Hons), MSc(Med), MBBCh, FCP(SA), Cert Neph(SA)

Division of Nephrology, Department of Internal Medicine

Faculty of Health Sciences

University of the Witwatersrand

Johannesburg, South Africa

E-mail address: gteckie@hotmail.com Cell: +27 835343181

ORCiD: 0000-0002-5508-5318

Dr Nasrin Goolam Mahyoodeen – MBChB, FCP(SA), Cert Endo and Metab(SA)

Division of Endocrinology, Department of Internal Medicine

Faculty of Health Sciences

University of the Witwatersrand

Johannesburg, South Africa

E-mail address: mahyoodeen@yahoo.com Cell: +27 842403314

ORCiD: 0000-0002-5939-752X

Plagiarism declaration

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

FACULTY OF HEALTH SCIENCES

PLAGIARISM DECLARATION TO BE SIGNED BY ALL HIGHER DEGREE STUDENTS

SENATE PLAGIARISM POLICY: APPENDIX ONE

I JOSE JACOB (Student number: 0701877) am a student registered for the degree of MMED in the academic year 2024.

I hereby declare the following:

- I am aware that plagiarism (the use of someone else's work without their permission and/or without acknowledging the original source) is wrong.
- I confirm that the work submitted for assessment for the above degree is my own unaided work except where I have explicitly indicated otherwise.
- I have followed the required conventions in referencing the thoughts and ideas of others.
- I understand that the University of the Witwatersrand may take disciplinary action against me if there is a belief that this is not my own unaided work or that I have failed to acknowledge the source of the ideas or words in my writing.
- I have included as an appendix a report from "Turnitin" (or other approved plagiarism detection) software indicating the level of plagiarism in my research document.

Signature: _____ Date: 12/09/2024

1

Author Contribution Statement and Agreement of Co-Authors

Title of Manuscript

Traditional And Non-Traditional Cardiovascular Risk Factors In The Chronic Dialysis Population At Chris Hani Baragwanath Academic Hospital And Sebokeng Provincial Hospital.

*Name of corresponding author

Dr Jose Jacob

Author contribution statement

Herewith all 3 authors declare that each author had made a significant contribution to this manuscript as detailed below, have seen and approved the final manuscript and have agreed to its submission.

*Dr Jose Jacob

Conceptual and research design, execution of research work, data collection, statistical analysis and interpretation of data, drafting manuscripts, final corrections and approval of final manuscript.

Dr Gloria Teckie

Conceptual and research design, supervision, interpretation of data, critical reviewing and editing of draft and approval of final manuscript.

Dr Nasrin Goolam Mahyoodeen

Conceptual and research design, supervision, interpretation of data, critical reviewing and editing of draft and approval of final manuscript.

Dr J Jacob Dr G Teckie Dr N Goolam Mahyoodeen

Acknowledgements

I would like to thank my supervisors, Dr G Teckie and Dr N Goolam Mahyoodeen for their kindness, understanding and guidance.

I would like to thank my wife Neethu for supporting me throughout this process.

Table Of Contents

List of figures

List of tables

Author Guidelines for Wits Journal of Clinical Medicine

WITS JOURNAL OF CLINICAL MEDICINE

Instructions for Authors

The Wits Journal of Clinical Medicine aims to provide peer reviewed publication of original articles, reviews, opinion papers, case and meeting reports dealing with all facets of Clinical Medicine practice and research. All articles will be independently peer-reviewed. Material accepted for publication is done on the undertaking that it has not been submitted for publication anywhere else.

SUBMISSIONS

All submissions should follow the style of the Journal and be clear and concise. The word count, including references, should not exceed 5000 words. Email to: rita.kruger@wits.ac.za

ARTICLE STRUCTURE

All articles should have a title page and include the following: a short descriptive title, authors surname and first name, email address for each author, a full postal address, telephone number, fax and email address for the corresponding author. The corresponding author should be identified with an asterix. All contributors will require an ORCiD which should also be submitted as an alphanumeric string. Please register at www.orcid.org if you don't have one already. The Editors may at a later date request validation authorisation for this publication.

THE TEXT

Please submit all text in Times New Roman, 12 point with 1.5 spacing in English (UK or South African). Text must be submitted as a Word document.

Tables and figures placement must be indicated in the text as part of the sentence example, see Table 1, or in parentheses (see Table 1). All tables and figures must include a descriptive

heading with appropriate attribution and permissions indicated. Figures and tables must be submitted separately from the Word document with the following file-naming convention (Lead author surname Fig.1.jpg) eg (Manga Fig. 2.jpg). Submit each figure electronically as a high resolution JPEG (at least 300 dpi). All tables and graphs (containing original data or which are not archival in nature) will be redrawn to suit the house style. Please ensure that all elements are included especially legends, scale indicators and all axes.

REFERENCES

References should be numbered in the order of appearance in the text (in parentheses after punctuation) and be presented according to Vancouver styling.

List first 5 authors. If more than 5 authors list the first three and add et al.

For articles:

Author A, Author B, Author XYZ. Title of article. Journal title abbreviated Year; volume: xx-zz.

Leurs R, Church MK, Taglialatela M. H1
-antihistamines:
inverse agonism, anti-inflammatory actions and cardiac effects. Clin Exp Allergy. 2002; 32(4):489-498.

For chapters in edited books:

Author A, Author BC. Title of the book chapter. In: Editor E, Editor FG, ed. Title of the book, X edn. Location: Publisher, year: xxx-zzz.

Glennon RA, Dukat M. Serotonin receptors and drugs affecting serotonergic neurotransmission. In: Williams DA, Lemke TL, editors. Foye's principles of medicinal chemistry. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2002.

For authored books:

Author A, Author B, Author C. Title. Edition. Location: Publisher; Year.

Rang HP, Dale MM, Ritter JM, Moore PK. Pharmacology.

5th ed. Edinburgh: Churchill Livingstone; 2003.

For all other reference queries eg datasets, websites and social media please consult the Vancouver style guide. When submitting articles to the Journal please try to adhere to the conventions outlined above as closely as possible.

STRUCTURE

The abstract (250 words) should outline the main purpose of the study, the key methods, the main results and conclusion.

The Introduction provides a background to the study and should be sufficient to permit non-specialists to understand the framework of the work. Include a well-defined statement regarding the purpose of the study. The methods: provide a description of the study design, all procedures, techniques and statistical analyses. The results: stipulate the study findings and ensure to cross-reference figures and tables. The discussion should elicit an interpretation of the study set against the background of current knowledge of the field and provide definitive conclusions.

Reviews will comprise a title page as above; an abstract (250 words), providing the setting of the review, any key messages and conclusions drawn. The body should be presented with headings and subheadings and lead to summary with conclusions to end. A few (2-5) key statements could be itemised in separate box. Acknowledgements, references, tables and figures must be as detailed above.

Abstract

Introduction

Patients with chronic kidney disease (CKD) are at risk for accelerated cardiovascular disease (CVD). There is evidence for the contribution of traditional and non-traditional risk factors to CVD in CKD. Non-traditional risk factors are under-recognised and poorly managed in CKD.

Methods

Clinical records for patients 18 years or older on chronic dialysis at two public hospitals in South Africa were retrospectively reviewed.

Results

There were 147 patients with a mean age of 43.7 years, 53% male and 98% black African in the cohort. The prevalence of hypertension was 85% with a mean systolic blood pressure of 148.0mmHg (±22.8) and a mean diastolic blood pressure of 93.4mmHg (±18.2), implying poor control in this cohort. The prevalence of diabetes mellitus was 5.5% and the mean body mass index was 24.5kg/m^2 (±4.5). The prevalence of anaemia was 41% with a mean haemoglobin of 10.6g/dL (±2.4). We found a high mean phosphate of 1.7mmol/L (±0.6), mean calcium of 2.2mmol/L (±0.3) and albumin 38.8g/L (±4.7) in the cohort. Patients on peritoneal dialysis (PD) had higher mean systolic (p=0.028) and diastolic blood pressure (p=0.004) compared to patients on haemodialysis (HD). Patients on PD had higher mean total cholesterol (p=0.001), PTH (p=0.028) and haemoglobin (p=0.015) levels compared to patients on HD. Patients on PD had lower mean albumin (p=0.001) and calcium (p=0.000) levels compared to patients on HD. When stratified by sex or HIV status, no significant differences in cardiovascular risk factors were found, except for a higher prevalence of smoking exposure in male patients.

Conclusion

In this cohort of mostly black African chronic dialysis patients, there was low prevalence of traditional cardiovascular risk factors except poorly controlled hypertension. We found high prevalence of anaemia and hyperphosphataemia. Those on PD had greater traditional and non-traditional risk factor burden. We recommend longitudinal follow-up studies evaluating effect of risk factor control on CVD outcomes to aid clinicians in managing this higher risk group.

Word Count: 311
Key words: Chronic kidney disease, cardiovascular disease, non-traditional risk factors

List Of Abbreviations

CKD:	Chronic kidney disease
GFR:	Glomerular filtration rate
SSA:	sub-Saharan Africa
HIV:	Human immunodeficiency virus
ESRD:	End stage renal disease
RRT:	Renal replacement therapy
CVD:	Cardiovascular diseases
DM:	Diabetes mellitus
CV:	Cardiovascular
BMI:	Body mass index
CHD:	Coronary heart disease
LDLc:	Low density lipoprotein cholesterol
TC:	Total cholesterol
TG:	Triglyceride
MI:	Myocardial infarction
CVA:	Cerebrovascular accident
SHARP:	Study of Heart and Renal Protection
KDIGO:	Kidney Disease | Improving Global Outcomes
HDLc:	High density lipoprotein cholesterol
HD:	Haemodialysis
ARIC:	Atherosclerosis Risk in Communities
PTH:	Parathyroid hormone
PD:	Peritoneal dialysis
HbA1c:	Glycated haemoglobin
CHBAH:	Chris Hani Baragwanath Academic Hospital
SPH:	Sebokeng Provincial Hospital
RAAS:	Renin angiotensin aldosterone system
VLDL:	Very low-density lipoprotein

Introduction

Chronic kidney disease (CKD) is defined as abnormalities of the kidney structure or function, present for more than three months, with implications for health. Such dysfunction may include pathological abnormalities or markers of kidney disease, and is classified based on cause, glomerular filtration rate (GFR) category or albuminuria category. (1)

In 2017, a joint statement from the American Society of Nephrology, European Renal Association, and International Society of Nephrology estimated a CKD prevalence of approximately 844 million people. (2) CKD is a major contributor to mortality and morbidity worldwide, with increasing incidence and prevalence in developing countries such as those in sub-Saharan Africa (SSA). (3, 4) This increase in prevalence is likely attributable to the growing burden of non-communicable diseases that contribute to development of CKD, together with the high prevalence of infectious diseases including Human Immunodeficiency Virus (HIV) as well as the increase in the elderly population. (3-6)

Cardiovascular diseases (CVD) are the leading cause of death in patients with CKD and studies have explored this relationship. (7-9) It has been shown that the CV risk of patients with ESRD is 5 to 500 times that of the general population when stratified by age and CV mortality in dialysis patients is 10 to 20 times higher than in the general population, despite being stratified by age, gender, race and the presence or absence of diabetes mellitus (DM). (10, 11) A meta-analysis by the Chronic Kidney Disease Prognosis Consortium has shown that even a modest reduction in estimated GFR or increase in albuminuria can significantly increase risk of all-cause mortality and CV mortality, both independent of each other, and of other CV risk factors. (12) CKD is an independent risk factor for CVD and a significant cause of premature mortality.

Traditional Cardiovascular Risk Factors

In 2010 CVD, CKD and DM were together responsible for 17.6 million deaths (33%) out of a total 52.8 million deaths worldwide and 63% of these deaths occurred in patients with traditional cardiovascular (CV) risk factors such as hypertension, hypercholesterolaemia, hyperglycaemia and high body mass index (BMI) after accounting for multi-causality. (13)

Hypertension remained the leading risk factor for deaths due to CVD, CKD and DM from 1980 to 2010 contributing to more than 40% of deaths in this combined group in 2010. (13) Hypertensive

nephropathy was found to be the leading cause of CKD in a low-income, predominantly black population in SSA. (14) Among pre-dialysis CKD patients in a private urban hospital in South Africa, black African patients exhibited a larger prevalence of hypertension and DM compared to other African patients. (15) It was further shown despite the use of intensive antihypertensive therapy, hypertension was more severe in black patients with CKD, and these findings align with other international studies looking at hypertension in African Americans. (15, 16) A bidirectional relationship exists between CKD and hypertension in which CKD can result from hypertension and CKD can lead to increased blood pressure, especially masked hypertension (elevated out of office blood pressure) and elevated nighttime blood pressure, thereby increasing CV risk. (14, 17) Major barriers exist to adequately lower systemic blood pressures in dialysis patients due to the multifactorial nature of hypertension in CKD, poor adherence to chronic medication, suboptimal dialysis delivery, poor salt and fluid restriction among others. (17, 18)

In a study by Jousilahti *et al,* traditional CV risk factors such as smoking, lipid abnormalities, hypertension, raised BMI and DM were assessed to explain the sex and age-related difference in coronary heart disease (CHD) risk. (19) Whilst a substantial part of the sex difference in CHD risk was attributed to the risk factor differences between males and females, CHD incidence was 3 times greater in men compared to women and risk of CHD in women increased significantly with age. (19) The authors postulate the difference is related to the actions of oestrogen on the endothelium and on lipid and glucose metabolism with increased cardioprotective effects in younger women in whom higher oestrogen levels occur. (19)

The Study of Heart and Renal Protection (SHARP) randomised trial has demonstrated benefit in the use of low-density lipoprotein cholesterol (LDLc) lowering agents (simvastatin and ezitimibe) to reduce atherosclerotic events in CKD stage 3a to 5. This translated to a 17% risk reduction in the primary outcome of major atherosclerotic events, which included MI, non-haemmorrhagic stroke or need for revascularization. (20) The SHARP trial failed to show benefit in CV outcomes in patients who were dialysis dependent. (20) The Kidney Disease: Improving Global Outcomes (KDIGO) organisation guidelines on lipid management in CKD therefore do not recommend the addition of statin or statin plus ezitimibe treatment in patients on dialysis. (1, 21) In line with KDIGO guidelines, the European Society of Cardiology/European Atherosclerosis Society have recommended the use of statin or statin plus ezitimibe combination in CKD stage 3 to 5 who are non-dialysis dependant, the continuation of lipid lowering therapy in patients who are already on these drugs at the time of dialysis initiation, but not to initiate lipid lowering therapy in patients

already on dialysis who are free of atherosclerotic CVD. (22) The lipid profile in patients with both pre-dialysis and dialysis stages of CKD has been extensively studied in several clinical randomised control trials. Patients with non-dialysis dependent CKD have a reduced high density lipoprotein cholesterol (HDLc) level and high triglyceride (TG) level, with a normal or even reduced LDLc level. Although LDLc is not usually raised in CKD; the LDLc particles are smaller, denser and highly atherogenic, causing a morphologically different plaque in patients with CKD. (23) There are paradoxical associations between dyslipidaemia and CVD related mortality in the haemodialysis (HD) population. (20, 24) In a study by Chang *et al*, an elevated TG:HDLc ratio was associated with reduced CV mortality and improved overall survival in patients on chronic HD. (25) One of the proposed theories is that the presence of malnutrition and inflammation in chronic HD patients accounts for the reduced total cholesterol (TC) and TG levels and also drives mortality. (24)

Non-traditional Cardiovascular Risk Factors

Non-traditional risk factors for CVD in patients with CKD have been identified and contribute to the increased risk of mortality and CV events, even at modest reductions of estimated GFR. Several of these non-traditional risk factors have been identified. These include anaemia, (26) abnormal calcium/phosphate metabolism, (27, 28) hypoalbuminaemia, (26) inflammation and oxidative stress, (10, 29) hyperhomocysteinaemia, (30) malnutrition, HIV (31-34) endothelial dysfunction, (27, 28, 35, 36) and other dialysis related factors. (37-39)

Anaemia

Anaemia is a well-established chronic complication of CKD because of reduced erythropoietin levels, chronic inflammation, iron deficiency and blood loss, among many other causes. (26, 40, 41) In a systematic review and meta-analysis looking at prevalence and predictors of anaemia in CKD patients in SSA, there was a pooled prevalence of anaemia of approximately 60% with advanced CKD stage, female sex, DM and a history of HD being significantly associated with the presence of anaemia.(42) In a multiethnic CKD population attending a renal outpatient clinic in Johannesburg, there was a 43% prevalence of anaemia with a higher prevalence in the black and mixed ethnic groups compared with white and Indian/Asian patients. (43) Low haemoglobin in patients with CKD had a strong association with risk of CVD in the Atherosclerosis Risk in Communities (ARIC) study. (26) It is hypothesised that with concomitant deranged renal function and low haemoglobin concentration, increased cardiac workload and reduced myocardial oxygen supply occur, thereby increasing the risk of CV events. (26) In a prospective cohort study by Iimori *et al,* anaemic patients with CKD had an increased all-cause mortality with an adjusted hazard ratio (HR) of 3.37 (95%

confidence interval, 1.76-6.44) and CVD-related mortality with an adjusted HR of 3.64 (95% confidence interval, 1.36-9.73). (44) A large placebo-controlled trial examining the effects of increasing haemoglobin to a level of 13g/dL with darbepoetin alfa showed no reduction in risk of cardiovascular and kidney outcomes in CKD stage 3-4 patients with DM. (45) This trial also showed an increased risk for stroke, venous thromboembolic events and mortality in patients with malignancy who were on darbepoeitin alfa. (45)

Chronic Kidney Disease-Mineral Bone Disorder

Chronic Kidney Disease-Mineral Bone Disorder studies have shown that dysfunction in calcium and phosphate homeostasis results in increased CV risk (28, 46) by inducing and promoting vascular intimal and medial calcification, which in turn result in atherosclerotic plaque development and reduced vascular compliance. (41, 47) Furthermore, coronary artery plaques can rupture resulting in cardiac events and arterial stiffness resulting from poor vessel wall compliance causes cardiac remodelling and left ventricular hypertrophy. (30, 36, 41) Elevated levels of fibroblast growth factor-23 (FGF-23), a bone-derived hormone that regulates phosphate excretion together with parathyroid hormone (PTH), has been strongly linked with myocardial fibrosis, endothelial dysfunction, arterial stiffness and results in increased CV risk in CKD. (48, 49) While normal calcium and phosphate levels are maintained in early CKD by compensatory increases in PTH and FGF-23, these mechanisms are overwhelmed in late CKD resulting in secondary and tertiary hyperparathyroidism. (50) Results from a study that pooled data from a nationally represented database of chronic HD patients in the United States has shown an increase in the relative risk of mortality with a raised serum phosphate and raised serum calcium concentration, both independent CV risk factors. (27) Elevated serum parathyroid hormone (PTH) concentration was also found to be a contributor to CV mortality in this cohort, although the relationship was not as strong as that in hyperphosphataemia and hypercalcaemia. (27) Studies have shown greater phosphate clearance in patients on HD, with higher time-averaged phosphate concentration in patients on peritoneal dialysis (PD). (51, 52) Some of the features of the phosphate molecule which make it less suitable for peritoneal clearance include its negative charge which is shared by capillary walls and interstitial matrix, protein binding and formation of salts with calcium, magnesium and sodium in blood, and it requires transmembrane active transporters which have a slow transfer rate across cell membranes. (53, 54)

Hypoalbuminaemia

Hypoalbuminaemia has been shown to be a risk factor for cardiac mortality in dialysis patients, independent of other traditional CV risk factors. (55, 56) The pathogenesis of hypoalbuminaemia in increasing cardiac mortality is not fully understood, but is hypothesised to be related to malnutrition

and inflammation.(57) Albumin is a negative acute phase reactant and hypoalbuminaemia is also found in non-benign lesions, glomerulonephritides, HIV and liver disease. This, together with the persistent inflammatory state of CKD contributes to a pro-atherogenic environment. (29, 55, 56) This may lead to the sequalae of endothelial damage, vascular calcification and CVD.

Inflammation

Inflammation in CKD is closely linked to the development of CVD. (29, 58) Decreased clearance of inflammatory mediators in ESRD along with increased production of pro-inflammatory cytokines and activation of inflammatory processes due to uraemia, elevated arterial blood pressure, pulse pressure, increased truncal fat mass and fluid overload in ESRD are some of the pathological mechanisms in which inflammation is stimulated and propagated. (29, 59) In addition, various acute and chronic infectious causes also contribute to chronic inflammation in patients on chronic dialysis. (29) Oguntola *et al*. demonstrated worse overall CV risk in black South Africans on PD compared to HD and pre-dialysis CKD patients and hypothesised that inflammation, retained uraemic toxins and the use of conventional glucose-based PD fluids which may have contributed to hyperinsulinaemia could explain the increased risk. (37)

Human Immunodeficiency Virus

HIV infection has been shown to be a significant non-traditional CV risk factor. The burden of CKD in HIV results from factors such as HIV glomerulonephropathies, immune activation and endothelial dysfunction as well as toxicities from drugs. (31, 32, 60) In a study by George *et al*, decrease in GFR in a cohort of HIV infected patients resulted in an increased risk of CV events, irrespective of traditional CV risk factors and this link can be explained by mechanisms such as chronic inflammation, immune activation and endothelial dysfunction in people living with HIV. (32, 34) In a private dialysis cohort in South Africa; longer hospital stays, higher infection rates which included vascular access infections and tuberculosis, lower albumin and haemoglobin levels were found in black HIV positive patients compared to the HIV negative patients. (61)

Other dialysis and transplant-related factors

Dialysis-related factors such as inflammation associated with chronic catheter usage for dialysis access, poor biocompatibility, back leakage of dialysate across dialyser membranes, peritonitis and dialysis catheter related infections in PD are associated with increased CV risk. (29, 38, 39) Patients on PD who are chronically exposed to glucose containing dialysate fluid are at a greater risk of

having a raised BMI, higher glycated haemoglobin (HbA1c), TC and LDLc. (24, 37) Renal transplant recipients have a higher risk of CV events than the general population, but this risk is lower than for patients on dialysis. (62) There are several factors that contribute to this additional risk, over and above the traditional risk factors. Some of these risk factors are due to the potent immunosuppressive therapy necessary to prevent graft rejection, which may predispose to the development of multiple CV risk factors like diabetes, uncontrolled hypertension, dyslipidaemia and obesity. (63) An important cause of anaemia in post-transplant patients, in addition to nutritional deficiency and on-going renal dysfunction, may be the use of myelosuppressive drugs such as azathioprine and mycophenolate mofetil. (63)

The main objective of this study was to report on the demographic, clinical and biochemical characteristics of the chronic dialysis population at two South African public hospitals and to report on the prevalence and risk factor control of traditional CV risk factors (smoking history, BMI, hypertension and its control, diabetes mellitus and glycaemic control and dyslipidaemia) and non-traditional risk factors (anaemia, hyper-phosphataemia, hyper-calcaemia, PTH level and HIV status) in the cohort.

Methodology

This was a retrospective, descriptive review of clinical records of patients on chronic HD and PD at Chris Hani Baragwanath Academic Hospital (CHBAH) and Sebokeng Provincial Hospital (SPH). This study included patients 18 years or older who are on the chronic dialysis program, on either HD or PD. The sample size consisted of all the patients who had been on dialysis for at least three months at the respective centres at the time of data collection between 1 December 2019 to 31 January 2020. Those who were not on dialysis for a minimum of three months and those who had incomplete clinical and biochemical records were excluded. A written informed consent form was administered to those eligible (Appendix B).

The most recent records for all patients eligible for the study were used to collect data within the parameters of the data collection sheet (Appendix B). Demographic information such as patient age, sex, race, HIV status, details of aetiology and of comorbid conditions were collected from the clinical records. Clinical information such as once-off blood pressure, weight and height from the most recent dialysis visit were collected. Glycaemic control was estimated with the use of a random capillary glucose measurement and from the most recent HbA1c levels. Haematological tests such as haemoglobin level, ferritin and transferrin saturation results were obtained from patient records. All

biochemical values including lipid studies, uric acid, calcium, phosphate, albumin, PTH levels were obtained from the biannual blood investigations that chronic HD and PD patients undergo as part of routine investigation and management. Medication history was also collected from the patient records and from prescriptions issued to patients for the investigation period.

Data was entered into an electronic worksheet (Microsoft Excel). Descriptive statistics for continuous variables were presented as mean ± standard deviation (SD) or median and interquartile ranges (IQR) for continuous variables, if normally distributed or skewed respectively. Categorical data was reported using proportions. Categorical variables were compared between groups using the $\chi 2$ test. Continuous variables were compared between groups using Students unpaired t-test (if normally distributed) and the Mann U Whitney test (if skewed). Data was analysed using SPSS Statistics version 25. A p-value of ≤ 0.05 was considered as statistically significant.

Ethics

The University of Witwatersrand Human Research Ethics Committee approved this study (Certificate number: M200160).

Results

A total of 150 chronic dialysis patients were identified. One patient was excluded due to not meeting inclusion criteria of a minimum of 3 months on chronic dialysis and two patients declined to participate in the study. The mean age of the 147 patients in this study was 43.7 years, with 53% being male and 98% black African (Table 1). PD was utilised by 42% of the cohort, and 58% of patients were on HD. The predominant vascular access method used by the majority of patients on HD (77%) was an arteriovenous graft/fistula. The prevalence of hypertension in this population was high (85%) and there was a low prevalence of smoking history and HIV at 11% and 17% respectively (Table 1). The mean systolic blood pressure was 148mmHg (±22.8) and mean diastolic blood pressure was 93mmHg (±18.2). The mean BMI for the population was 24.5kg/m^2 (±4.5) (Table 1). On average, there was a haemoglobin level of 10.6g/dL (±2.4) and PTH level of 78 pmol/L (±76.8) (Table 1).

Table 1 Demographic, clinical and biochemical characteristics of chronic dialysis patients

Characteristics of chronic dialysis population	N	Mean (±SD)or(N%)
Age(years)	147	43.7(± 11.4)
Black African	147	144(98.0)
Male	147	78(53.1)
Dialysis Access	147	
Permcath (Tunnelled haemodialysis catheter)		16(10.9)
Arteriovenous Graft/Fistula		66(44.9)
Temporary dialysis catheter (non-tunnelled)		4(2.7)
Tenckhoff catheter (Peritoneal dialysis)		61(41.5)
Previous Renal Transplant	147	9(6.1)
Smoking history	147	16(10.9)
Hypertension	146	124(84.9)
Diabetes Mellitus	146	8(5.5)
HIV positive	147	25(17.0)
Dyslipidaemia	146	10(6.9)
CVA	146	2(1.4)
Body Mass Index(kg/m^2)	143	24.5(±4.5)
Systolic Blood Pressure(mmHg)	146	148.0(±22.8)
Diastolic Blood pressure(mmHg)	146	93.4(±18.2)
Haemoglobin(g/dL)	133	10.6(±2.4)
Ferritin(ng/mL)	122	528.3(±427.8)
Calcium(mmol/L)	132	2.2(±0.3)
Phosphate(mmol/L)	130	1.7(±0.6)
Parathyroid hormone(pmol/L)	124	78.0(±76.8)
Albumin(g/L)	94	38.8(±4.7)
Total Cholesterol(mmol/L)	67	4.0(±1.1)
Triglyceride(mmol/L)	15	1.2(±0.8)
LDL Cholesterol(mmol/L)	15	2.0(±0.6)
HDL Cholesterol(mmol/L)	15	1.2(±0.3)
Alkaline phosphatase(IU/L)	17	175.1(±190.1)
Uric acid(mmol/L)	9	0.4(±0.1)
HbA1c(%)	6	7.5(±2.4)

Postulated Aetiology of End Stage Renal Disease

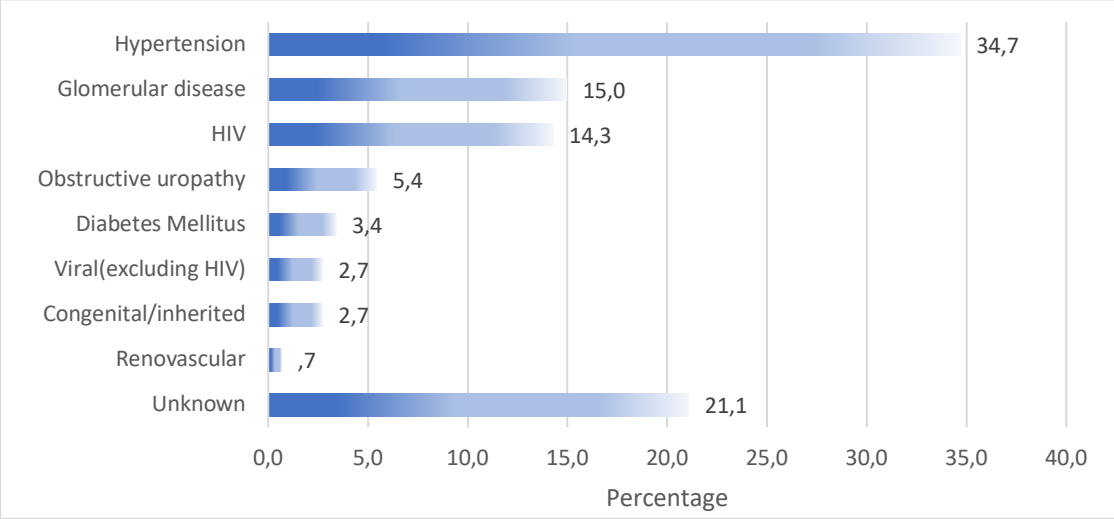

Figure 1: Postulated aetiology of end stage renal disease

As seen in Figure 1 above, hypertension is the main postulated aetiology of ESRD in our cohort at 35%. HIV accounted for 14% of ESRD and diabetes mellitus was suspected to be the aetiology in only 3% of patients.

Chronic Medication History of Patients with End Stage Renal Disease

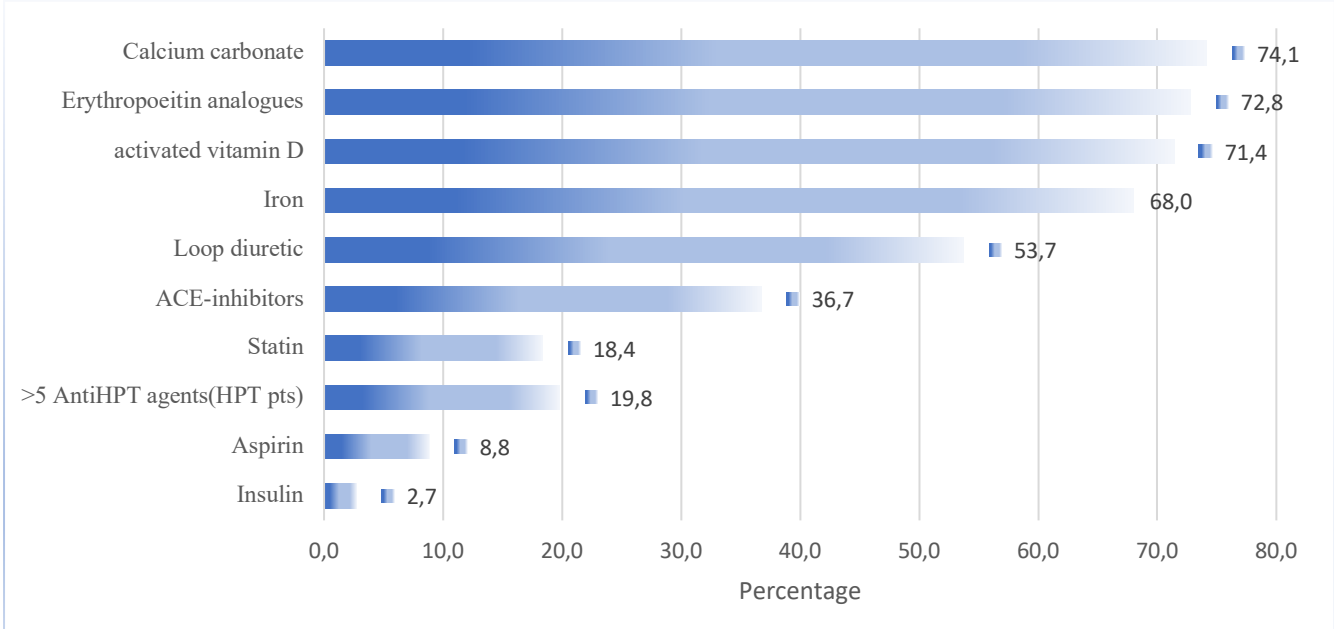

Figure 2: Medication history of patients with end stage renal disease

Among the patients known with hypertension, 20% were on more than 5 anti-hypertensive agents. Erythropoietin analogues and intravenous iron were utilised by 73% and 68% patients respectively.

Calcium carbonate was prescribed for 74% patients, and 71% patients were prescribed activated vitamin D therapy. Aspirin was used by 8.9% of the cohort, while 18.3% of patients were on statin therapy (Figure 2).

Risk Factor Profile by Dialysis Modality

There were no significant differences in age when comparing HD and PD patients (Table 2). However, there were significantly higher mean systolic (p=0.028) and diastolic blood pressures (p=0.004) in PD versus HD patients (Figure 3). Patients on HD had lower mean haemoglobin levels compared with patients on PD (p=0.015). HDLc levels were found to be lower (p=0.020), and TC levels were found to be higher (p=0.001) in PD when compared to HD patients (Figure 4). Mean LDLc levels were also higher in patients on PD, however this was not statistically significant. Mean albumin levels were lower in patients on PD (p=0.001) (Figure 5). While patients on PD had higher mean PTH levels (p=0.028) (Figure 6), mean serum calcium levels were higher in HD patients (p=0.000) (Table 2).

Table 2 Risk factors by dialysis modality

	N	Haemodialysis	Peritoneal dialysis	P-value
Age	**147**	44.4(±11.7)	42.7(±11.0)	0.376
Hypertension	**124**	69 (81.2)	55 (90.2)	0.163
Diabetes Mellitus	**8**	4 (4.7)	4 (6.6)	0.720
HIV	**25**	12 (14.0)	13 (21.3)	0.270
Dyslipidaemia	**10**	3 (3.5)	7 (11.5)	0.094
CVA	**2**	2 (2.4)	0 (0)	0.510
Smoking history	**16**	10 (11.6)	6 (9.9)	0.794
BMI(kg/m^2)	**144**	24.0(±4.0)	25.1(±5.2)	0.147
Systolic blood pressure(mmHg)	**146**	144.5(±22.2)	152.9(±22.9)	**0.028**
Diastolic blood pressure(mmHg)	**146**	89.8(±19.2)	98.4(±15.4)	**0.004**
Haemoglobin(g/dL)	**133**	10.2(±2.4)	11.2(±2.1)	**0.015**
Calcium(mmol/L)	**132**	2.3(±0.2)	2.1(±0.3)	**0.000**
Phosphate(mmol/L)	**130**	1.7(±0.8)	1.8(±0.6)	0.465
Parathyroid hormone(pmol/L)	**124**	65.1(±58.8)	101.5(±98.1)	**0.028**
Total cholesterol(mmol/L)	**67**	3.7(±0.7)	5.1(±1.3)	**0.001**
Triglyceride(mmol/L)	**15**	1.0(±0.4)	2.1(±1.6)	0.379
LDL cholesterol(mmol/L)	**15**	1.9(±0.6)	2.5(±0.3)	0.074
HDL cholesterol(mmol/L)	**15**	1.3(±0.3)	0.9(±0.2)	**0.020**
Albumin(g/L)	**95**	40.1(±4.6)	36.9(±4.3)	**0.001**
Uric acid(mmol/L)	**9**	0.4(±0.1)	-	-
HbA1c(%)	**6**	5.8(±0.1)	8.3(±2.6)	0.148

*Results shown as mean(±SD) or N(%)

Risk Factor Profile by Sex Category

There were no significant differences between male and female patients except for a higher prevalence of smoking exposure in males (p=0.003) (Table 3). Mean TC, PTH, calcium and phosphate were numerically higher in female patients, however this did not reach statistical significance.

Table 3 Risk factors by sex category

	N	Male	Female	P-value
Age(years)	**147**	44.9(±11.8)	42.4(±10.9)	0.177
Hypertension	**124**	68 (87.2)	56 (82.4)	0.490
Diabetes Mellitus	**8**	5 (6.4)	3 (4.4)	0.724
HIV	**25**	13 (16.7)	12 (17.4)	1.000
Dyslipidaemia	**10**	5 (6.4)	5 (7.4)	1.000
CVA	**2**	1 (1.3)	1 (1.5)	1.000
Smoking history	**16**	14 (18.0)	2 (2.9)	**0.003**
BMI(kg/m^2)	**143**	24.2(±4.6)	24.8±(4.4)	0.476
Systolic blood pressure(mmHg)	**146**	149.7(±23.4)	146.0(±22.1)	0.326
Diastolic blood pressure(mmHg)	**146**	94.0(±16.9)	92.7(±19.6)	0.661
Haemoglobin(g/dL)	**133**	10.8(±2.2)	10.3(±2.6)	0.291
Calcium(mmol/L)	**132**	2.29(±0.3)	2.3(±0.3)	0.560
Phosphate(mmol/L)	**130**	1.7(±0.8)	1.7(±0.7)	0.560
Parathyroid hormone(pmol/L)	**124**	69.2(±60.6)	88.7(±92.1)	0.176
Total cholesterol(mmol/L)	**67**	3.8(±1.0)	4.3(±1.0)	0.051
Triglyceride(mmol/L)	**15**	1.3(±1.2)	1.2(±0.3)	0.955
LDL cholesterol(mmol/L)	**15**	2.0(±0.5)	2.0(±0.8)	0.960
HDL cholesterol(mmol/L)	**15**	1.1(±0.2)	1.3(±0.3)	0.162
Albumin(g/L)	**95**	39.1(±4.6)	38.3(±4.8)	0.437
Uric acid(mmol/L)	**9**	0.4(±0.1)	0.3(±0.1)	0.566
HbA1c(%)	**6**	7.2(±2.8)	8.1(±2.3)	0.716

*Results shown as mean(±SD) or N(%)

Risk Factor Profile by HIV Status

There were no significant differences between patients living with HIV and those who were HIV negative (Table 4).

Table 4 Risk factors by HIV status

	N	HIV positive	HIV negative	P-value
Age(years)	**147**	45.4(±7.1)	43.4(±12.1)	0.250
Hypertension	**124**	23(92.0)	101(83.5)	0.369
Diabetes Mellitus	**8**	1(4.0)	7(5.8)	1.000
Dyslipidaemia	**10**	2(8.0)	8(6.6)	0.681
CVA	**2**	0 (0)	2 (1.7)	1.000
Smoking history	**16**	3(12.0)	13(10.7)	0.737
BMI(kg/m^2)	**143**	24.0(±7.1)	24.6(±3.9)	0.621
Systolic blood pressure(mmHg)	**146**	148.1(±21.1)	148.0(±23.2)	0.986
Diastolic blood pressure(mmHg)	**146**	92.1(±13.9)	93.6(±18.9)	0.710
Haemoglobin(g/dL)	**133**	10.6(±2.0)	10.6(±2.4)	0.955
Calcium(mmol/L)	**132**	2.2(±0.2)	2.2(±0.3)	0.930
Phosphate(mmol/L)	**130**	1.6(±0.7)	1.7(±0.7)	0.589
Parathyroid hormone(pmol/L)	**124**	79.0(±71.5)	77.8(±78.0)	0.949
Total cholesterol(mmol/L)	**67**	4.0(±0.6)	4.0(±1.1)	0.905
Triglyceride(mmol/L)	**15**	1.6(±1.2)	1.0(±0.4)	0.152
LDL cholesterol(mmol/L)	**15**	2.2(±0.4)	1.8(±0.7)	0.335
HDL cholesterol(mmol/L)	**15**	1.1(±0.3)	1.3(±0.3)	0.292
Albumin(g/L)	**95**	39.7(±4.1)	38.6(±4.8)	0.416
Uric acid(mmol/L)	**9**	0.3(±0)	0.4(±0.1)	0.785
HbA1c(%)	**6**	5.8(±0)	7.8(±2.6)	0.519

*Results shown as mean(±SD) or N(%)

Discussion

This is a retrospective review of clinical records of a chronic dialysis cohort consisting of predominantly young black African patients from two South African regional public hospitals. The limited resources for renal replacement therapy (RRT) in our setting demand a strict selection criteria which results in the inclusion of mostly young and otherwise healthy adults with ESRD. In our cohort consisting of 98% black Africans, the characteristics of patients on RRT were similar to the black African dialysis cohort in a private hospital in Johannesburg with the exception of the prevalence of DM. (15)

Traditional risk factors assessed in our study included hypertension, DM, obesity, smoking history and dyslipidaemia. Aetiology of ESRD was determined by the treating renal team, mainly on clinical grounds, with a small minority being based on renal biopsies. Postulated aetiology of ESRD was hypertension in 35% of our cohort but we found an overall prevalence of hypertension of 85%. This is possibly due to the bi-directional nature of hypertension which is both a cause and complication in CKD. (17) Patients with DM accounted for only 6% of the cohort and the prevalence of obesity in our cohort was 8%, however this cannot be generalised to other cohorts due to the patient selection criteria for chronic dialysis. While a BMI more than 35 kg/m^2 excludes entry into the chronic dialysis program, there are patients who gain weight while on chronic dialysis. Overweight and obese patients are assisted with weight loss interventions, and the importance of weight management is emphasised to increase the patients' chances of transplant. Current or previous smoking history was observed in 11% of patients.

We found overall inadequate control of hypertension in our cohort. Higher prevalence and severity of hypertension in Americans of African descent compared to other racial groups is well documented and is recognised as a one of the most important risk factors for CVD in this population. (16) In the study by Hsu *et al*. in Johannesburg, black patients with CKD had more severe hypertension and were on more intensive antihypertensive therapy in comparison to non-black counterparts. (15) Around 20% of the hypertensive patients in our study were prescribed more than five antihypertensive medications.

While only 10 patients were formally diagnosed with dyslipidaemia, 46% of those assessed had elevated TC levels with a mean of 4.0 mmol/L (±1.1) and 66% of those assessed had high LDLc levels with a mean of 2.0 mmol/L (±0.6). Statin usage was documented in 18% of patients. This discrepancy is likely related to data from large randomised controlled trials which show clinical

benefit of statins in patients on chronic dialysis are uncertain, (64) consequently KDIGO guidelines do not recommend initiation of lipid lowering therapy in most patients on chronic dialysis, but to continue statin treatment if previously initiated. (21)

Anaemia is a significant non-traditional CV risk factor in CKD patients and the prevalence of anaemia in SSA is estimated to be around 59% among CKD patients. (42) Anaemic patients with CKD have increased all-cause and CVD-related mortality. (26, 44) The mean haemoglobin level in our cohort was 10.6 g/l (±2.4) which is comparable to the median haemoglobin level for the black African dialysis cohort in the study by Hsu *et al*. (15) Haemoglobin level less than 10 g/dL was found in 41% of our cohort. This is in contrast to a study conducted in Uganda by Babua et al, where the prevalence of anaemia in ESRD was 85%. (33) This discrepancy could be attributed to the utilisation of intravenous iron (68%) and erythropoietin (73%) in our cohort compared to the Ugandan cohort where only 1% of patients were on erythropoietin and iron sucrose. (33) Of note, KDIGO guidelines recommend the initiation of erythropoiesis-stimulating agents in patients on chronic dialysis with haemoglobin levels between 9 g/dL and 10 g/dL after addressing other causes of anaemia such as iron deficiency. (65) The KDIGO guidelines also do not recommend the use of erythropoiesis-stimulating agents to maintain haemoglobin concentration above 11.5 g/dL to limit adverse effects such as CVA, vascular access thrombosis and hypertension which are potential harms attributed to erythropoiesis-stimulating agents. (65)

While we found a higher median phosphate level of 1.6 mmol/L in our cohort compared to the black African cohort (1.3 mmol/L) in the study by Hsu *et al.* and a Limpopo cohort (1.4 mmol/L) of predominantly rural dwelling chronic dialysis patients in a study by Tamayo Isla *et al*., calcium levels were similar in all three cohorts. (15, 39) Mean albumin levels were within the normal range in our cohort and the Johannesburg cohort, (15) but the cohort from Limpopo had a lower mean albumin level, which the authors attribute to a baseline malnourished state. (39)

This study demonstrated elevated mean systolic and diastolic blood pressures in patients on PD compared to HD. International studies have shown higher arterial blood pressures, volume overload and left ventricular hypertrophy in patients on PD compared to HD. (66-68) Elevated blood pressures could be due to infrequent measurement of blood pressure with resultant suboptimal treatment of hypertension or inadequate delivery of prescribed dialysis in patients on PD. (37) In contrast to PD, patients on HD are assessed thrice weekly at their HD sessions often with adjustments being made to their chronic prescriptions.

Patients on PD with DM in our study had higher HAb1c levels compared to those on HD, but this result was not statistically significant. This is likely due to the utilisation of conventional glucose-based dialysate for PD in our setting. Studies have shown continuous glucose exposure from dialysate predispose patients on PD to hyperinsulinaemia and the consequences such as glucose intolerance, obesity and lipid abnormalities. (37, 68)

We found statistically significant higher mean TC levels and lower mean HDLc levels in patients on PD compared to HD. Although mean LDLc levels were higher in patients on PD in our cohort, this result was not statistically significant. A multicentre study in patients on PD in Portugal showed worse lipid profiles with greater mean levels of TG, TC and LDLc as well as higher mean PTH levels, but comparable mean calcium level in comparison with our cohort. (59) A study comparing non-diabetic patients on PD, HD, pre-dialysis CKD patients and healthy controls at a large urban hospital in South Africa by Oguntola *et al.* in 2019 showed lower albumin level and elevated TC and LDLc levels in patients on PD compared with both patients on HD and with CKD stage 3. (37) The hypothesised mechanisms for elevated LDLc include albumin loss in dialysate, glucose absorption from dialysate and hepatic overproduction of Very Low-Density Lipoprotein (VLDL), from which LDLc is derived. (68, 69)

Like the cohort in the study by Tamayo Isla *et al.*, we observed lower mean haemoglobin levels in patients on HD compared with patients on PD. (39) Potential causes for this observation include blood loss in the dialysis circuit, more frequent heparin use, phlebotomy and more frequent invasive procedures related to dialysis access when compared with patients on PD. This may also be due to more rapid loss of residual renal function on HD compared with PD. (51) Reduced residual renal function in patients on HD could also be related to the utilisation of a 'PD first' approach in state hospitals, where patients are mostly only transitioned to HD after PD failure.

We found patients on PD had significantly elevated mean PTH levels and lower mean albumin and calcium levels compared to patients on HD. Studies demonstrate that patients on PD were more likely to have higher LDLc concentration, low albumin, hyperphosphatemia and elevated PTH level compared to patients on HD. (37, 53, 68-70) There was a high utilization rate of calcium based phosphate binders and activated vitamin D therapy in our cohort, and this was comparable to that of the black African dialysis cohort in the study by Hsu *et al*. (15)

Male patients on chronic dialysis in our study had a higher prevalence of smoking exposure. The Global Adult Tobacco Survey South Africa 2021 report found 41% of males and 12% of females were active tobacco smokers. (71) A meta-analysis published in 2025 estimating smoking prevalence in Sub-Saharan Africa have reported a similar higher prevalence in males compared to females and this may be due to social or cultural attitudes that stipulate lower expectations for smoking among females. (72) We found no other significant differences in the clinical and biochemical characteristics of the cohort when stratified by sex.

There were also no significant differences in the clinical and biochemical characteristics of the cohort when stratified by HIV status. In the South African study by Fabian *et al*. there were no significant differences in the incidence of CVA or CHD between HIV positive and HIV negative chronic dialysis patient groups over a 5 year period, despite an incompletely suppressed HIV viral load in 51% of patients on treatment. (61) Similarly, in a retrospective population based cohort of patients started on dialysis between 1996 and 2022 in Australia and New Zealand, there were no significant differences in the lifetime prevalence figures of CVA, CHD and peripheral vascular disease between HIV positive and HIV negative patients. (73) While we did not assess response to anti-retroviral treatment in this study, factors improving adherence in the chronic dialysis cohort may include frequent monitoring of HIV viral load and improved access to care as well as frequent contact with medical personnel and provision of health education at each dialysis session.

The limitations of this study were its retrospective nature, and that some data were missing from patient records. Sample sizes were limited by the number of available slots for patients requiring chronic dialysis. Furthermore, due to the selection criteria for RRT in the public sector, which selects young healthy patients, the results may not be readily generalisable to other dialysis cohorts.

Conclusion

CKD patients are at high risk for accelerated CVD. This study looked at the prevalence and control of traditional and non-traditional risk factors in a chronic dialysis cohort. In this cohort of mostly black African chronic dialysis patients, there was a high prevalence of inadequately controlled hypertension. Anaemia is a common non-traditional CV risk factor and is multifactorial in CKD. Our cohort had a mean haemoglobin level of 10.6 g/l (±2.4) with high utilisation of both intravenous iron and erythropoietin.

When assessing traditional CV risk factors, we found that patients on PD had higher mean systolic and diastolic blood pressures, worse DM control and lipid profile compared to patients on HD. The use of conventional glucose-based dialysate, albumin loss in the dialysate leading to hepatic overproduction of VLDL with eventual LDLc formation, inadequate dialysis delivery and poor adherence to medication, fluid and salt restriction are factors that could be contributing to excess CV risk in patients on PD. While haemoglobin was within the range recommended by KDIGO for chronic dialysis patients on erythropoietin-stimulating agents, patients on HD had a lower mean haemoglobin level. Patients on PD had a lower mean albumin and calcium level and a higher mean PTH level. Poor phosphate clearance compared to HD and inflammation related to non-biocompatible dialysate in addition to albumin loss in the dialysate are factors contributing to additional CV risk in PD. When stratified by sex or HIV status, no significant differences in CV risk factors were found, except for a higher prevalence of smoking exposure in male patients.

This study showed patients on PD had greater overall CV risk burden. Longitudinal follow-up studies are recommended to evaluate how risk factors and their control affect CVD outcomes in this higher risk population. Improved knowledge of common risk factors will aid clinicians managing dialysis patients in optimising care.

References

1.Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;2024;105(4s):S117-s314.

2.Jager KJ, Kovesdy C, Langham R, et al. A single number for advocacy and communication—worldwide more than 850 million individuals have kidney diseases. Nephrology Dialysis Transplantation. 2019;34(11):1803-5.

3.KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney int. 2013;3(1):5-14.

4.Stanifer JW, Jing B, Tolan S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. The Lancet Global Health. 2014;2(3):e174-e81.

5.Jha V, Garcia-Garcia G, Iseki K, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260-72.

6.Hill NR, Fatoba ST, Oke JL, et al. Global Prevalence of Chronic Kidney Disease – A Systematic Review and Meta-Analysis. PLOS ONE. 2016;11(7):e0158765.

7.Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. The New England journal of medicine. 2004;351(13):1296-305.

8.Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339-52.

9.Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. Circulation. 2021;143(11):1157-72.

10.Zoccali C. Traditional and emerging cardiovascular and renal risk factors: an epidemiologic perspective. Kidney Int. 2006;70(1):26-33.

11.Foley RN, Parfrey PS, Sarnak MJ. Epidemiology of cardiovascular disease in chronic renal disease. Journal of the American Society of Nephrology : JASN. 1998;9(12 Suppl):S16-23.

12.van der Velde M, Matsushita K, Coresh J, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney Int. 2011;79(12):1341-52.

13.The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. The lancet Diabetes & endocrinology. 2014;2:634-47.

14.Twala NMS, Tade G, Dessein PH, Teckie G. Causes of Chronic Kidney Disease and Their Associations with Cardiovascular Risk and Disease in a Sub-Saharan Low-Income Population. International journal of nephrology and renovascular disease. 2024;17:175-95.

15.Hsu H-C, Robinson C, Woodiwiss AJ, Norton GR, Dessein PH. Cardiovascular Risk Factor Profiles and Disease in Black Compared to Other Africans with Chronic Kidney Disease. International Journal of Nephrology. 2021;2021(1):8876363.

16.Carnethon MR, Pu J, Howard G, et al. Cardiovascular Health in African Americans: A Scientific Statement From the American Heart Association. Circulation. 2017;136(21):e393-e423.

17.Burnier M, Damianaki A. Hypertension as Cardiovascular Risk Factor in Chronic Kidney Disease. Circulation Research. 2023;132(8):1050-63.

18.Bakris GL, Burkart JM, Weinhandl ED, McCullough PA, Kraus MA. Intensive Hemodialysis, Blood Pressure, and Antihypertensive Medication Use. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2016;68(5s1):S15-s23.

19.Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, Age, Cardiovascular Risk Factors, and Coronary Heart Disease. Circulation. 1999;99:1165-72.

20.Baigent C, Landray MJ, Reith C, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181-92.

21.Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group M. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney Int. 2014;85(6):1303-9.

22.Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). European Heart Journal. 2019;41(1):111-88.

23.Drueke TB, Massy ZA. Atherosclerosis in CKD: differences from the general population. Nat Rev Nephrol. 2010;6(12):723-35.

24.Mikolasevic I, Zutelija M, Mavrinac V, Orlic L. Dyslipidemia in patients with chronic kidney disease: etiology and management. International journal of nephrology and renovascular disease. 2017;10:35-45.

25.Chang TI, Streja E, Soohoo M, et al. Association of Serum Triglyceride to HDL Cholesterol Ratio with All-Cause and Cardiovascular Mortality in Incident Hemodialysis Patients. Clin J Am Soc Nephrol. 2017;12(4):591-602.

26.Ishigami J, Grams ME, Naik RP, et al. Hemoglobin, Albuminuria, and Kidney Function in Cardiovascular Risk: The ARIC (Atherosclerosis Risk in Communities) Study. J Am Heart Assoc. 2018;7(2).

27.Block GA, Klassen PS, Lazarus JM, et al. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. Journal of the American Society of Nephrology : JASN. 2004;15(8):2208-18.

28.McGovern AP, de Lusignan S, van Vlymen J, et al. Serum Phosphate as a Risk Factor for Cardiovascular Events in People with and without Chronic Kidney Disease: A Large Community Based Cohort Study. PLoS ONE. 2013;8:e74996.

29.Dai L, Golembiewska E, Lindholm B, Stenvinkel P. End-Stage Renal Disease, Inflammation and Cardiovascular Outcomes. In: Ronco C, editor. Expanded Hemodialysis: Innovative Clinical Approach in Dialysis. 191: S.Karger AG; 2017. p. 0.

30.Hajhosseiny R, Khavandi K, Goldsmith DJ. Cardiovascular disease in chronic kidney disease: untying the Gordian knot. Int J Clin Pract. 2013;67(1):14-31.

31.Campbell LJ, Ibrahim F, Fisher M, et al. Spectrum of chronic kidney disease in HIV-infected patients. HIV Med. 2009;10(6):329-36.

32.Nou E, Lo J, Grinspoon SK. Inflammation, immune activation, and cardiovascular disease in HIV. AIDS. 2016;30(10):1495-509.

33.Babua C, Kalyesubula R, Okello E, et al. Cardiovascular risk factors among patients with chronic kidney disease attending a tertiary hospital in Uganda. Cardiovasc J Afr. 2015;26.

34.George E, Lucas GM, Nadkarni GN, et al. Kidney function and the risk of cardiovascular events in HIV-1-infected patients. AIDS. 2010;24(3):387-94.

35.Covic A, Vervloet M, Massy ZA, et al. Bone and mineral disorders in chronic kidney disease: implications for cardiovascular health and ageing in the general population. The lancet Diabetes & endocrinology. 2018;6(4):319-31.

36.Ritter CS, Slatopolsky E. In-Depth Review Phosphate Toxicity in CKD: The Killer among Us. Clin J Am Soc Nephrol. 2016;11:1088-100.

37.Oguntola SO, Hassan MO, Duarte R, et al. Atherosclerotic vascular disease is more prevalent among black ESKD patients on long-term CAPD in South Africa. BMC Nephrology. 2019;20(1):399.

38.Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in U.S. hemodialysis patients. Kidney Int. 2001;60(4):1443-51.

39.Tamayo Isla RA, Ameh OI, Mapiye D, et al. Baseline Predictors of Mortality among Predominantly Rural-Dwelling End-Stage Renal Disease Patients on Chronic Dialysis Therapies in Limpopo, South Africa. PLOS ONE. 2016;11(6):e0156642.

40.Pancha Mbouemboue O, Danbe OD, Tangyi Tamanji M, Ngoufack JO. Frequency of Specific Cardiovascular Disease Risk Factors among Cameroonian Patients on Dialysis: The Cases of Anaemia, Inflammation, Phosphate, and Calcium. Cardiology research and practice. 2016;2016:5031927.

41.Yerram P, Karuparthi PR, Hesemann L, Horst J, Whaley-Connell A. Chronic kidney disease and cardiovascular risk.

42.Taderegew MM, Wondie A, Terefe TF, et al. Anemia and its predictors among chronic kidney disease patients in Sub-Saharan African countries: A systematic review and meta-analysis. PLoS One. 2023;18(2):e0280817.

43.Nalado AM, Mahlangu JN, Waziri B, et al. Ethnic prevalence of anemia and predictors of anemia among chronic kidney disease patients at a tertiary hospital in Johannesburg, South Africa. International journal of nephrology and renovascular disease. 2019;12:19-32.

44.Iimori S, Naito S, Noda Y, et al. Anaemia management and mortality risk in newly visiting patients with chronic kidney disease in Japan: The CKD-ROUTE study. Nephrology (Carlton). 2015;20(9):601-8.

45.Pfeffer MA, Burdmann EA, Chen C-Y, et al. A Trial of Darbepoetin Alfa in Type 2 Diabetes and Chronic Kidney Disease. New England Journal of Medicine. 2009;361(21):2019-32.

46.Obi Y, Mehrotra R, Rivara MB, et al. Hidden Hypercalcemia and Mortality Risk in Incident Hemodialysis Patients. The Journal of Clinical Endocrinology & Metabolism. 2016;101(6):2440-9.

47.Ribeiro C, Penido MG, Guimaraes MM, et al. Parathyroid ultrasonography and bone metabolic profile of patients on dialysis with hyperparathyroidism. World journal of nephrology. 2016;5(5):437-47.

48.Vallianou NG, Mitesh S, Gkogkou A, Geladari E. Chronic Kidney Disease and Cardiovascular Disease: Is there Any Relationship? Curr Cardiol Rev. 2019;15(1):55-63.

49.Subbiah AK, Chhabra YK, Mahajan S. Cardiovascular disease in patients with chronic kidney disease: a neglected subgroup. Heart Asia. 2016;8(2):56-61.

50.Moorthi RN, Moe SM. CKD-mineral and bone disorder: core curriculum 2011. American journal of kidney diseases : the official journal of the National Kidney Foundation. 2011;58(6):1022-36.

51.Wang AY, Lai KN. The importance of residual renal function in dialysis patients. Kidney Int. 2006;69(10):1726-32.

52.Evenepoel P, Wolf M. A balanced view of calcium and phosphate homeostasis in chronic kidney disease. 2013.

53.Evenepoel P, Meijers BK, Bammens B, et al. Phosphorus metabolism in peritoneal dialysis- and haemodialysis-treated patients. Nephrol Dial Transplant. 2016;31(9):1508-14.

54.Cernaro V, Calderone M, Gembillo G, et al. Phosphate Control in Peritoneal Dialysis Patients: Issues, Solutions, and Open Questions. Nutrients. 2023;15(14).

55.Foley RN, Parfrey PS, Harnett JD, et al. Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. Journal of the American Society of Nephrology : JASN. 1996;7(5):728-36.

56.Shah NR, Dumler F. Hypoalbuminaemia – A Marker of Cardiovascular Disease in Patients with Chronic Kidney Disease Stages II - IV. International Journal of Medical Sciences. 2008:366-70.

57.Cardoso A, Branco C, Sant'Ana M, et al. Hypoalbuminaemia and One-Year Mortality in Haemodialysis Patients with Heart Failure: A Cohort Analysis. J Clin Med. 2021;10(19).

58.Kadatane SP, Satariano M, Massey M, Mongan K, Raina R. The Role of Inflammation in CKD. Cells. 2023;12(12).

59.Neves M, Machado S, Rodrigues L, et al. Cardiovascular risk in peritoneal dialysis - a Portuguese multicenter study. Nefrologia : publicacion oficial de la Sociedad Espanola Nefrologia. 2014;34(2):205-11.

60.Moosa MR, Van der Walt I, Naicker S, Meyers AM. Important causes of chronic kidney disease in South Africa. S Afr Med J. 2015;105(4):2681.

61.Fabian J, Maher HA, Clark C, et al. Morbidity and mortality of black HIV-positive patients with end-stage kidney disease receiving chronic haemodialysis in South Africa. S Afr Med J. 2015;105(2):110-4.

62.de Mattos AM, Prather J, Olyaei AJ, et al. Cardiovascular events following renal transplantation: role of traditional and transplant-specific risk factors. Kidney Int. 2006;70(4):757-64.

63.Neale J, Smith AC. Cardiovascular risk factors following renal transplant. World J Transplant. 2015;5(4):183-95.

64.Sharp Collaborative G. Study of Heart and Renal Protection (SHARP): randomized trial to assess the effects of lowering low-density lipoprotein cholesterol among 9,438 patients with chronic kidney disease. Am Heart J. 2010;160(5):785-94 e10.

65.McMurray J, Parfrey P, Adamson JW, et al. Kidney disease: Improving global outcomes (KDIGO) anemia work group. KDIGO clinical practice guideline for anemia in chronic kidney disease. Kidney International Supplements. 2012:279-335.

66.Enia G, Mallamaci F, Benedetto FA, et al. Long-term CAPD patients are volume expanded and display more severe left ventricular hypertrophy than haemodialysis patients. Nephrology Dialysis Transplantation. 2001;16(7):1459-64.

67.Van Biesen W, Williams JD, Covic AC, et al. Fluid status in peritoneal dialysis patients: the European Body Composition Monitoring (EuroBCM) study cohort. PLoS One. 2011;6(2):e17148.

68.Zamiah S, Draman CR, Seman MR, et al. The cardiovascular risk factor profiles among end-stage renal failure patients treated with continuous ambulatory peritoneal dialysis and intermittent hemodialysis. Saudi J Kidney Dis Transpl. 2018;29(1):114-9.

69.Prichard SS. Management of hyperlipidemia in patients on peritoneal dialysis: current approaches. Kidney Int Suppl. 2006(103):S115-7.

70.Ellam T. Confounded complexity: vitamin d, parathyroid hormone, and metabolic syndrome in peritoneal dialysis. Perit Dial Int. 2014;34(4):333-7.

71.National Department of Health GATS (Global Adult Tobacco Survey) Fact Sheet, South Africa. [Accessed on 04 September 2025];2024 [Available from: https://www.health.gov.za/wp-content/uploads/2022/05/Global-Adult-Tobacco-Survey-GATS-SA_FS-Populated__28-April-2022.pdf.

72.Belete H, Mekonen T, Connor JP, et al. Tobacco smoking in Sub-Saharan Africa: A systematic review and meta-analysis. Drug and Alcohol Review. 2025;44(4):1079-91.

73.Hunter-Dickson M, Huang A, Drak D, Zheng C, Gracey D. Outcomes of Dialysis Patients Living With HIV in Australia and New Zealand: A Cohort Study Using the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA). Nephrology (Carlton). 2025;30(9):e70115.

Appendix A – Accepted Protocol

Traditional and Non-traditional Cardiovascular Risk Factors in the Chronic Dialysis Population at Chris Hani Baragwanath Academic Hospital and Sebokeng Provincial Hospital

Student: Dr Jose Jacob
Student Number: 0701877X
Masters Degree in Medicine

Supervisors
Dr Gloria Teckie, Division of Nephrology, Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital, Johannesburg
Dr Nasrin Goolam Mahyoodeen, Division of Endocrinology, Department of Internal Medicine, Chris Hani Baragwanath Academic Hospital, Johannesburg

Research Statement
The link between chronic kidney disease (CKD) and cardiovascular disease (CVD) is well established. Even from the earliest stages of CKD, patients are at significant risk from CVD related events such as cerebrovascular accident, myocardial infarction and peripheral vascular disease. There is significant data that point to the relatively extensive contribution of non-traditional risk factors to CVD in those patients with CKD. While the traditional risk factor profile of patients with CKD is frequently monitored and optimised, there exists a whole array of non-traditional or 'novel' risk factors; which often go unrecognised and unaddressed. This audit will assess and evaluate the prevalence of selected traditional and non-traditional cardiovascular (CV) risk factors in the chronic dialysis population of Chris Hani Baragwanath Academic Hospital (CHBAH) and Sebokeng Provincial Hospital (SPH).

Introduction
Chronic kidney disease is defined as abnormalities of the kidney structure or function, present for more than three months, with implications for health. Such dysfunction may include pathological abnormalities or markers of kidney disease, and is classified based on cause, glomerular filtration rate (GFR) category or albuminuria category (1).
The GFR categories are:

1 - normal or high [>90 ml/min/1.73m^2];

2 - mildly decreased [60-89 ml/min/1.73m^2];

3a - mild to moderately decreased [45-59 ml/min/1.73m^2];

3b -moderately to severely decreased [30-44 ml/min/1.73m^2];

4 - severely decreased [15-29 ml/min/1.73m^2]; and

5 - advanced renal failure [<15 ml/min/1.73m^2] or End stage Renal Disease (ESRD)(1).

CKD affects around 8-16% of the population worldwide (2), with a smaller proportion falling into the category of CKD 5 or End Stage Renal Disease (ESRD). It is estimated that the prevalence of CKD is around 14% in sub-Saharan Africa (SSA), and this number will continue to rise (2). Furthermore, it is also estimated that by 2030, more than 70% of the people with ESRD will be from low-income countries such as those in SSA (2).

The major causes of CKD in most developed countries include diabetes and hypertension (3). The importance of CKD and other non-communicable diseases is becoming increasingly recognised in low to middle income countries. An epidemiological study by Stanifer *et al* describes the wide range of causes for CKD in SSA (2). Alongside the growing burden of chronic diseases of lifestyle or non-communicable diseases; infectious diseases, glomerulonephritis and environmental toxins contribute to the development of CKD in developing countries (2, 3). This is because of the rapid rate of urbanisation, changes in lifestyle and an ageing population overlapping with high prevalence of infectious diseases in developing countries (2, 3). CKD is also a common chronic complication of Human Immunodeficiency Virus (HIV) infection; which is highly prevalent in SSA, with around 64% of the 36.7 million people living with HIV residing in SSA (2). The burden of CKD in HIV results from the occurrence of HIV glomerulonephropathies as well as toxicities from drugs (4).

In 2010 - CVD, CKD and diabetes were together responsible for 17.6 million deaths (33%) out of a total 52.8 million deaths worldwide (5). Background high blood pressure, high serum cholesterol, high blood sugar and high Body Mass Index (BMI) accounted for 63% of the deaths after accounting for multi-causality (5). Thus, a significant proportion of premature mortality can be attributed to these traditional risk factors. Cigarette smoking is a modifiable traditional CV risk factor, which results in a pro-atherogenic and pro-thrombotic state due to increased oxidative stress (6). Hyper-uricaemia is a CV risk factor, and is associated with hypertension and progressive loss of renal function in the general population (7). In a study by Jousilahti *et al,* CV risk factors such as smoking, total cholesterol, HDL cholesterol, blood pressure, BMI and diabetes were assessed to explain the

sex and age-related difference in coronary heart disease (CHD) risk (8). Whilst a substantial part of the sex difference in CHD risk was attributed to the risk factor differences between males and females, CHD incidence was 3 times greater in men compared to women and risk of CHD increased significantly with age (8).

In 1836, Richard Bright was the first physician to hypothesise and report on the secondary cardiovascular changes in patients with primary renal disease (9). Since then, several studies have explored the relationship between CVD and CKD with the implications of improving outcomes and treatment in both conditions. CVDs are the leading cause of death in patients with CKD, even before their progression to ESRD (10). It has been shown that up to 50% of patients with ESRD will die as a result of cardiovascular events and that the cardiovascular mortality rate of patients with ESRD is 5 to 500 times that of the general population (11).

To detect associations between estimated GFR and risk of all cause mortality, cardiovascular events and hospitalization; Go *et al* conducted a study in a group consisting of 1,120,295 adults who were not being dialysed or had undergone kidney transplantation. After adjusting for differences in social and demographic factors as well as for other co-morbid illnesses; including proteinuria and whether or not dialysis was initiated; the risk of death from any cause in patients with CKD stage 3a increased by 17% and this risk was increased by 600% in those with CKD stage 5. The adjusted risk of cardiovascular events also increased by 43% and 343% in those with CKD stage 3a and in those with CKD stage 5 respectively (10).

Similarly, a meta-analysis by the Chronic Kidney Disease Prognosis Consortium has shown that even a modest reduction in estimated GFR or increase in albuminuria can significantly increase risk of all cause mortality and cardiovascular mortality, both independent of each other, and of other cardiovascular risk factors (12). A number of other studies that have demonstrated this association between CKD and CVD, in which the risk of CVD and cardiovascular mortality is exponentially greater in those with CKD and/or proteinuria (13), independent of traditional risk factors (11). It then would follow that there are ‘non-traditional risk factors’ present in patients with CKD, and these factors contribute to the increased risk of mortality and cardiovascular events, even at modest reductions of estimated GFR.

Several of these non-traditional risk factors have been identified and the interactions whereby they increase cardiovascular mortality have been described. These include anaemia (14), hypo-

albuminaemia (14), hyper-homocysteinaemia (13), malnutrition, inflammation and oxidative stress (11, 15), abnormal calcium/phosphate metabolism, HIV (16-19) and endothelial dysfunction (20-23).

Anaemia is a well-established chronic complication of CKD and is usually as a result of chronic inflammation, iron deficiency and reduced erythropoietin levels (14, 24, 25). In the Atherosclerosis Risk in Communities study (ARIC), low haemoglobin in patients with CKD had a strong association with risk of CVD (14). It is hypothesised that with concomitant deranged renal function and low haemoglobin concentration; increased cardiac work load and reduced myocardial oxygen supply can occur, thereby increasing the risk of cardiovascular events (14). In a prospective cohort study by Iimori *et al,* anaemic patients with CKD had an increased all-cause mortality with an adjusted hazard ratio of 3.37(95% confidence interval, 1.76-6.44) and CVD-related mortality with an adjusted hazard ratio of 3.64 (95% confidence interval, 1.36-9.73) (26). The prevalence of iron deficiency in this subgroup of pre-dialysis patients with CKD was also investigated and iron deficiency was shown to be associated with a higher mortality risk with an adjusted hazard ratio of 3.11(95% confidence interval 1.21-8.01) (26).

Chronic Kidney Disease-Mineral Bone Disorder (CKD-MBD) is a complex and not fully understood process. Results from a study that pooled data from a nationally represented database of chronic haemodialysis patients in the United States (US) has shown an increase in the relative risk of mortality with a raised serum phosphate and raised serum calcium concentration, both independent of each other and of other cardiovascular risk factors (20). Elevated serum parathyroid hormone concentration was also found to be a contributor to cardiovascular mortality in this cohort, although the relationship was not as strong as that in hyper-phosphataemia and hyper-calcaemia (20). Several studies have shown that dysfunction in calcium and phosphate homeostasis results in increased cardiovascular risk (22) by inducing and promoting vascular intimal and medial calcifications, which in turn result in atherosclerotic plaque development and reduced vascular compliance respectively (25, 27). Further, coronary artery plaques can rupture resulting in cardiac events and arterial stiffness resulting from poor vessel wall compliance causes cardiac remodeling and left ventricular hypertrophy (13, 23, 25).

Low-grade inflammation, which has been implicated in the progression of atherosclerosis, is a feature of CKD from the earlier stages of the disease and the aetiology of this condition appears to be multifactorial (15). Some of the factors that result in inflammation in CKD include increased production and reduced renal clearance of pro-inflammatory cytokines as a response to uraemia, pro-

oxidants and increased oxidative stress from haemodialysis (15). On-going chronic inflammation in CKD can occur as a result of other comorbidities such as fluid overload, obesity, hypertension, congestive heart failure and infections such as hepatitis (13, 15). HIV has also been shown to be a significant non-traditional CV risk factor. In a study by George *et al*, decrease in GFR in a cohort of HIV infected patients resulted in an increased risk of CV events, irrespective of traditional CV risk factors and this link can be explained by mechanisms such as chronic inflammation, immune activation and endothelial dysfunction in HIV (18, 19).

Hypo-albuminaemia has been shown to be a risk factor for cardiac mortality in dialysis patients, independent of other traditional CV risk factors (28, 29). The pathogenesis of hypo-albuminaemia in increasing cardiac mortality is not fully understood. However, it is known that albumin is a negative acute phase reactant, and that CKD is a persistent inflammatory state, which is pro-atherogenic (15, 28, 29).

It is well established that an elevated low density lipoprotein (LDL) cholesterol, total cholesterol and triglyceride levels increase CV risk in the general population (30) and that by lowering LDL cholesterol with statins, the risk of myocardial infarction and stroke can be reduced (30). The Study of Heart and Renal Protection (SHARP) randomised trial has demonstrated benefit in the use of LDL lowering simvastatin and ezitimibe to reduce atherosclerotic events in a CKD population within the categories of CKD stage 3a to CKD stage 5. This translated to a 17% risk reduction in the primary outcome of major atherosclerotic event, which included myocardial infarction, non-haemmorrhagic stroke or any revascularization (31). The SHARP trial, however, failed to show benefit in CV outcomes in patients who are dialysis dependent (31). The KDIGO guidelines on lipid management in CKD therefore do not recommend the addition of statin or statin plus ezitimibe treatment in patients on dialysis (32). The lipid profile in patients with both pre- dialysis and dialysis stages of CKD has been extensively studied in several clinical randomised control trials. Patients with non dialysis dependent CKD have a reduced HDL cholesterol level and high triglyceride level, with a normal or even reduced LDL cholesterol level. Although LDL cholesterol is not usually raised in CKD; the LDL cholesterol particles are smaller, denser and highly atherogenic, thereby causing a morphologically different plaque in patients with CKD (33). There are paradoxical associations between dyslipidaemia and CVD related mortality in the haemodialysis population (31, 34). In a study by Chang *et al*, an elevated triglyceride to HDL cholesterol ratio was associated with reduced CV mortality and improved overall survival in patients on chronic haemodialysis (30). This association has many explanations, with one being that of ‘reverse epidemiology’ or ‘reverse

causation', where one of the proposed theories is the presence of malnutrition and inflammation in chronic haemodialysis patients, which accounts for the reduced total cholesterol and triglyceride levels and also drives mortality (34).

There are also several dialysis related factors that contribute to increased CV risk. On-going chronic inflammation is associated with catheter usage for dialysis access, poor biocompatibility of dialyser membranes, exposure to endotoxins and back leakage of dialysate across the dialysate membranes (15). In an observational study based on US registry data, central venous catheters and arteriovenous grafts were associated with higher risk of cardiac mortality in diabetics when compared to arteriovenous fistulae, independent of comorbid conditions (35). In peritoneal dialysis, recurrent peritonitis and peritoneal dialysis catheter-related infections contribute to inflammation (15). Peritoneal dialysis patients are at greater risk for increased triglyceride levels due to the absorption of glucose from dialysis fluid. This induces hepatic lipoprotein synthesis and enhanced hepatic very low density lipoprotein (VLDL) synthesis in response to insulin (34). Another contributory mechanism may be the increased hepatic production of lipoproteins in response to the loss of plasma proteins in the dialysate (34). Further, it has been shown that patients receiving peritoneal dialysis are at a greater risk of having a raised BMI, higher HbA1c, total and LDL cholesterol levels as a result of long term exposure to glucose containing dialysis fluid (36).

Renal transplant recipients (RTR) are at a higher risk of fatal and non-fatal CV events than the general population, but this risk is lower than that of patients who remain on dialysis (37). There are several factors that contribute to this additional risk, over and above the traditional risk factors. Some of these risk factors are due to the potent immunosuppressive therapy necessary to prevent graft rejection in RTR's. Immunosuppressants in the post-transplant period predispose patients to the development of multiple CVS risk factors like diabetes, uncontrolled hypertension, dyslipidaemia and obesity (38). An important cause of anaemia in post transplant patients, in addition to nutritional deficiency and on-going renal dysfunction may be the use of myelosuppressive drugs such as azathioprine and MMF (38).

The increased CV risk in CKD is well described (10, 39-42). However, there remains a gap in the understanding of CVD with respect to the contribution of traditional and non-traditional risk factors in SSA, and in South Africa in particular. There is a need for more research into these risk factors and a greater awareness of the non-traditional risk factors, development of standardised monitoring tools to diagnose and monitor non-traditional risk factors as well as identification of therapeutic

targets whereby CV risk and progressive loss of renal function can be reduced. In a systematic review by Major *et al*, non-traditional risk factors such as serum albumin, phosphate, uric acid, haemoglobin and left ventricular hypertrophy were found to be statistically significant in their relationship with future CV events (42). However, there is a paucity of randomised control trials to evaluate the rate of reduction in CV events upon modifying these non-traditional risk factors.

In this retrospective study, the prevalence and risk factor control of specific traditional and non-traditional risk factors in a South African chronic dialysis population will be described and analysed. The information from this study can be used to develop protocols to close the gap between evidence and practice as well as highlight the necessity for interventional trials to assess the effect of modifying non-traditional risk factors in the CKD population.

Aim

To assess and evaluate the prevalence of traditional and non-traditional CV risk factors in the chronic dialysis populations of CHBAH and SPH.

Objectives

1. To describe the characteristics of the dialysis population at CHBAH and SPH with respect to aetiology of ESRD, modality of dialysis, previous renal transplant, medication history and previous myocardial infarction or cerebrovascular accident.
2. To assess the prevalence of traditional CV risk factors in the chronic dialysis patients at CHBAH and SPH, with respect to demographic, clinical and biochemical parameters including age, sex, race, weight, smoking history, hypertension and its control, diabetes mellitus and glycaemic control, hyper-triglyceridaemia and hyper-cholesterolaemia.
3. To assess the prevalence of non-traditional CV risk factors in the chronic dialysis patients at CHBAH and SPH, with respect to the following parameters: anaemia, hyper-phosphataemia, hyper-calcaemia, parathyroid hormone level, HIV status.

Methods

Study Design

This will be a retrospective, descriptive review of clinical records.

Sites

The Renal Dialysis Units at CHBAH and SPH.

Study Population and Samples

This study will be conducted at the Renal Units at CHBAH and SPH and will include patients 18 years or older and on either haemodialysis or peritoneal dialysis on the chronic dialysis program. The sample size will consist of all the patients receiving dialysis at the respective centres at the time of data collection.

Eligibility Criteria

Inclusion Criteria

1. Age above 18 years.
2. All patients who have been on either haemodialysis or peritoneal dialysis for more than 3 months.

Exclusion Criteria

1. Patients who have been on chronic dialysis for a period shorter than three months.
2. Patients with no or suboptimal clinical and biochemical data records.

Data collection

The most recent records for all patients eligible for the study will be used to collect data within the parameters of the data collection sheet (Appendix A). Patient age, sex, race, HIV status, details of aetiology and of comorbid conditions will be collected from the clinical records. Once off blood pressure, weight and height from the most recent dialysis visit will be collected. Glycaemic control will be estimated with the use of a random blood glucose measurement and from the most recent HbA1c levels. Haemoglobin level, ferritin and transferrin saturation results will be collected to assess for anaemia and iron deficiency. All biochemical values including lipid studies, uric acid,

calcium, phosphate, albumin, parathyroid hormone levels will be obtained from the biannual blood investigations that chronic haemodialysis and peritoneal dialysis patients undergo as part of routine investigation and management.

Statistical analysis

Data will be entered into an electronic worksheet (Microsoft Excel). Descriptive statistics for continuous variables will be presented as mean ± standard deviation (SD) or median and interquartile ranges (IQR) for normal or skewed data, respectively. Categorical data will be reported using proportions. Categorical variables will be compared between groups using the χ^2 test. Continuous variables will be compared between groups using Students unpaired t-test (if normally distributed) and the Mann U Whitney test (if skewed). Data will be analysed with a data analysis program, with assistance from a statistician.

Ethics

This study will be carried out at Renal Units at CHBAH and SPH, in fulfillment of the requirements of the Masters in Medicine degree. Ethics approval will be sought from the University of Witwatersrand Human Research Ethics Committee and permission will be sought from the hospital authorities. Written permission to access patient files from the Renal Clinics will be obtained from the Head of Department of the respective Renal Units.

Unique patient identifications numbers will be used on the data collection sheet to protect the identity of the study participants. The patients file number and the information from the file will be kept on a separate sheet for further reference use if needed. No remuneration will be given for the medical records reviewed. Findings will be published in academic journals and will be used to help improve the care and management of patients with CKD.

Limitations

1. The study population is small, as the number of patients eligible for the chronic dialysis program is limited by the number of available slots for dialysis.

2. The results are not readily generalisable to a general population, or to a different cohort of patients with ESRD, as the patient selection to the dialysis program ensures that only those with the most favourable prognosis are considered for chronic dialysis. This is as a result of the renal replacement therapy (RRT) selection protocol necessitated by the resource-constrained setting in which this study is based. The CVD in this cohort may thus be under-represented as only patients with the most favourable profile meet the rigorous selection criteria for RRT.

3. Only the parameters routinely assessed as part of the clinic's protocols will be evaluated. Other relevant parameters such as socio-economic status and anthropometry, among others, will not be assessed.

Timing

	April 2018	May 2018	June 2018	July 2018	August 2018	Sept 2018	Oct 2018	Nov 2018	Dec 2018
Proposal and ethics approval									
Data Collection									
Data Analysis									
Thesis write-up									
Submission for marking									

Funding

As this is a retrospective study, all laboratory tests were part of routine follow-up of patients in this cohort. Ancillary expenses including paper and printing costs will be borne by the researcher. Neither the patients nor the department will be required to bear any expenses.

References

1.KDIGO. CKD WORK GROUP. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Intern Suppl. 2013;3(1):1-150.
2.Stanifer JW, Jing B, Tolan S, Helmke N, Mukerjee R, Naicker S, et al. The epidemiology of chronic kidney disease in sub-Saharan Africa: a systematic review and meta-analysis. Lancet Glob Health. 2014;2(3):e174-e81.
3.Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260-72.
4.Moosa MR, Van der Walt I, Naicker S, Meyers AM. Important causes of chronic kidney disease in South Africa. S Afr Med J. 2015;105(4):2681.
5.The Global Burden of Metabolic Risk Factors for Chronic Diseases Collaboration. Cardiovascular disease, chronic kidney disease, and diabetes mortality burden of cardiometabolic risk factors from 1980 to 2010: a comparative risk assessment. Lancet Diabetes Endocrinol. 2014;2:634-47.
6.Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. J Am Coll Cardiol. 2004;43(10):1731-7.
7.Johnson RJ, Kang DH, Feig D, Kivlighn S, Kanellis J, Watanabe S, et al. Is there a pathogenetic role for uric acid in hypertension and cardiovascular and renal disease? Hypertension. 2003;41(6):1183-90.
8.Jousilahti P, Vartiainen E, Tuomilehto J, Puska P. Sex, Age, Cardiovascular Risk Factors, and Coronary Heart Disease. Circulation. 1999;99:1165-72.
9.Gansevoort RT, Correa-Rotter R, Hemmelgarn BR, Jafar TH, Heerspink HJ, Mann JF, et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet. 2013;382(9889):339-52.
10.Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.
11.Zoccali C. Traditional and emerging cardiovascular and renal risk factors: An epidemiologic perspective. Kidney international. 2006;70(1):26-33.
12.van der Velde M, Matsushita K, Coresh J, Astor BC, Woodward M, Levey A, et al. Lower estimated glomerular filtration rate and higher albuminuria are associated with all-cause and cardiovascular mortality. A collaborative meta-analysis of high-risk population cohorts. Kidney international. 2011(1523-1755).
13.Hajhosseiny R, Khavandi K, Goldsmith DJ. Cardiovascular disease in chronic kidney disease: untying the Gordian knot. Int J Clin Pract. 2013;67(1):14-31.

14.Ishigami J, Grams ME, Naik RP, Caughey MC, Loehr LR, Uchida S, et al. Hemoglobin, Albuminuria, and Kidney Function in Cardiovascular Risk: The ARIC (Atherosclerosis Risk in Communities) Study. J Am Heart Assoc 2018;7:e007209 DOI: 101161/JAHA117007209.
15.Dai L, Golembiewska E, Lindholm B, Stenvinkel P. End-Stage Renal Disease, Inflammation and Cardiovascular Outcomes. Contrib Nephrol. 2017;191:32-43.
16.Babua C, Kalyesubula R, Okello E, Kakande B, Sebatta E, Mungoma M, et al. Cardiovascular risk factors among patients with chronic kidney disease attending a tertiary hospital in uganda. Cardiovasc J Afr. 2015;26.
17.Campbell LJ, Ibrahim F, Fisher M, Holt SG, Hendry BM, Post FA. Spectrum of chronic kidney disease in HIV-infected patients. HIV Med. 2009;10(6):329-36.
18.Nou E, Lo J, Grinspoon SK. Inflammation, Immune Activation, and Cardiovascular Disease in HIV. AIDS (London, England). 2016;30(10):1495-509.
19.George E, Lucas GM, Nadkarni GN, Fine DM, Moore R, Atta MG. Kidney Function and the Risk of Cardiovascular Events in HIV-1 Infected Patients. AIDS (London, England). 2010;24(3):387-94.
20.Block GA, Klassen Ps Fau - Lazarus JM, Lazarus Jm Fau - Ofsthun N, Ofsthun N Fau - Lowrie EG, Lowrie Eg Fau - Chertow GM, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004(1046-6673).
21.Covic A, Vervloet M, Massy ZA, Torres PU, Goldsmith D, Brandenburg V, et al. Bone and mineral disorders in chronic kidney disease: implications for cardiovascular health and ageing in the general population. Lancet Diabetes Endocrinol. 2018;6(4):319-31.
22.McGovern AP, de Lusignan S, van Vlymen J, Liyanage H, Tomson CR, Gallagher H, et al. Serum Phosphate as a Risk Factor for Cardiovascular Events in People with and without Chronic Kidney Disease: A Large Community Based Cohort Study. PLoS ONE. 2013;8:e74996. doi: 10.1371/journal.pone.0074996.
23.Ritter CS, Slatopolsky E. In-Depth Review Phosphate Toxicity in CKD: The Killer among Us. Clin J Am Soc Nephrol. 2016;11:1088-100.
24.Pancha Mbouemboue O, Danbe OD, Tangyi Tamanji M, Ngoufack JO. Frequency of Specific Cardiovascular Disease Risk Factors among Cameroonian Patients on Dialysis: The Cases of Anaemia, Inflammation, Phosphate, and Calcium. Cardiol Res Pract 2016
http://dxdoiorg/101155/2016/5031927
. 2016.
25.Yerram P, Karuparthi PR, Hesemann L, Horst J, Whaley-Connell A. Chronic kidney disease and cardiovascular risk. J Am Soc Hypertens. 2007;1(3).

26.Iimori S, Naito S, Noda Y, Nishida H, Kihira H, Yui N, et al. Anaemia management and mortality risk in newly visiting patients with chronic kidney disease in Japan: The CKD-ROUTE study. Nephrology. 2015;20(9):601-8.
27.Ribeiro C, Penido MG, Guimaraes MM, Tavares Mde S, Souza B, Leite AF, et al. Parathyroid ultrasonography and bone metabolic profile of patients on dialysis with hyperparathyroidism. World J Nephrol. 2016;5(5):437-47.
28.Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. J Am Soc Nephrol. 1996;7(5):728-36.
29.Shah NR, Dumler F. Hypoalbuminaemia – A Marker of Cardiovascular Disease in Patients with Chronic Kidney Disease Stages II - IV. Int J Med Sci. 2008:366-70.
30.Chang TI, Streja E, Soohoo M, Kim TW, Rhee CM, Kovesdy CP, et al. Association of Serum Triglyceride to HDL Cholesterol Ratio with All-Cause and Cardiovascular Mortality in Incident Hemodialysis Patients. Clin J Am Soc Nephrol. 2017;12(4):591-602.
31.Baigent C, Landray M, Reith C, Dasgupta T, Emberson J, Herrington W, et al. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet. 2011;377(9784):2181-92.
32.Wanner C, Tonelli M, Kidney Disease: Improving Global Outcomes Lipid Guideline Development Work Group M. KDIGO Clinical Practice Guideline for Lipid Management in CKD: summary of recommendation statements and clinical approach to the patient. Kidney international. 2014;85(6):1303-9.
33.Drueke TB, Massy ZA. Atherosclerosis in CKD: differences from the general population. Nat Rev Nephrol. 2010;6(12):723-35.
34.Mikolasevic I, Zutelija M, Mavrinac V, Orlic L. Dyslipidemia in patients with chronic kidney disease: etiology and management. Int J Nephrol Renovasc Dis. 2017;10:35-45.
35.Dhingra RK, Young EW, Hulbert-Shearon TE, Leavey SF, Port FK. Type of vascular access and mortality in U.S. hemodialysis patients. Kidney international. 2001;60(4):1443-51.
36.Zamiah SAK, Draman C, Seman M, Safhan A, Rozalina R, Nik Ruzni N. The cardiovascular risk factor profiles among end-stage renal failure patients treated with continuous ambulatory peritoneal dialysis and intermittent hemodialysis. Saudi J Kidney Dis and Transpl. 2018;29(1):114-9.
37.de Mattos AM, Prather J, Olyaei AJ, Shibagaki Y, Keith DS, Mori M, et al. Cardiovascular events following renal transplantation: role of traditional and transplant-specific risk factors. Kidney international. 2006;70(4):757-64.

38.Neale J, Smith AC. Cardiovascular risk factors following renal transplant. World J Transplant. 2015;5(4):183-95.
39.Swanepoel CR, Swanepoel C. Chronic kidney disease is a risk factor for cardiovascular disease. SA Heart. 2007;4(3):36-41.
40.Thomas B, Matsushita K, Abate KH, Al-Aly Z, Arnlov J, Asayama K, et al. Global Cardiovascular and Renal Outcomes of Reduced GFR. J Am Soc Nephrol. 2017;28(7):2167-79.
41.Yerram P, Karuparthi PR, Hesemann L, Horst J, Whaley-Connell A. Chronic kidney disease and cardiovascular risk. J Am Soc Hypertens. 2007;1(3):178-84.
42.Major RW, Cheng MRI, Grant RA, Shantikumar S, Xu G, Oozeerally I, et al. Cardiovascular disease risk factors in chronic kidney disease: A systematic review and meta-analysis. PLoS One. 2018;13(3):e0192895.

Appendix B: Patient Information Leaflet And Data Collection Tool

Patient Information Leaflet

Patient study number:

Study title: Traditional and Non-Traditional Cardiovascular Risk Factors in the Chronic Dialysis Population at Chris Hani Baragwanath Academic Hospital and Sebokeng Provincial Hospital

Investigators and affiliations

1] Dr Jose Jacob - Department of Internal Medicine, University of Witwatersrand
2] Dr Gloria Teckie - Division of Nephrology, Department of Internal Medicine, University of Witwatersrand
3] Dr Nasrin Goolam Mahyoodeen - Division of Endocrinology, Department of Internal Medicine, University of Witwatersrand

Information sheet and Consent form

Good day, I am Jose Jacob, an internal medicine registrar at the University of Witwatersrand. I would like to provide you with information regarding a research study that is being undertaken at the renal units at Chris Hani Baragwanath Academic Hospital and Sebokeng Provincial Hospital.

After you have read and understood the study purpose, methods of data collection and maintaining confidentiality, benefits and risks to you as a potential participant, I would like to invite you to participate in this research study.

The purpose of the study is to determine the presence and evaluate the control of selected risk factors for cardiovascular disease in the dialysis population. For this purpose, the medical records kept at the respective renal units will be used to collect data under the categories specified in the data collection sheet (see Appendix B).

Your personal details will be kept safe at all times, and no identifying information will be published at any point.

There will be no risk to you from participating in this study. There will not be any additional hospital visits, longer waiting times at the clinic or any costs incurred or any remuneration from participating in this study. The benefits of this study include identifying gaps in the knowledge regarding

cardiovascular risk factors in chronic kidney disease as well as identifying modifiable risk factors which require improved control.

Please familiarise yourself with the above and feel free to contact me on 0837980080 with any questions or concerns about this study.

Informed Consent Form

Traditional and Non-Traditional Cardiovascular Risk Factors in the Chronic Dialysis Population at Chris Hani Baragwanath Academic Hospital and Sebokeng Provincial Hospital

I, (name)_____(surname)_____hereby confirm that I have been informed by the study investigator about the nature, conduct, benefits and risks of the study.

- I have received, read and understood the above written information (patient information leaflet and informed consent) regarding the study.
- I am aware that the results of the study will be anonymously processed into any research reports, presentations and/or journal articles.
- I am aware that the results of this study, including my personal details will be kept confidential.
- I understand that I may withdraw from this study at any point.
- I understand that if I have further questions about the study, the investigator will clarify these to me.
- I accept to participate in the study

Patient

Printed name _____signature/thumb print _____date _____ _____

Principal investigator

I herewith confirm that the above participant has been fully informed about the nature, conduct and risks of the above study.

Printed name _____signature_____ _____date_____ _____ _____

_____

Witness

Data Collection Sheet

Patient study number: Site:

Baseline data

Age:

Sex: Male ☐ Female ☐

Race: African ☐Indian/Asian☐Coloured ☐White☐

Dialysis modality: Haemodialysis ☐Peritoneal Dialysis ☐

Aetiology of ESRD: Diabetes ☐ Hypertension ☐ HIV ☐

Congenital/Inherited ☐ Glomerular disease ☐

Viral(Excluding HIV) ☐ Renovascular ☐ Obstructive uropathy ☐

Chronic pyelonephritis ☐ Toxin/Drug-Related ☐Other/unknown ☐

Previous renal transplant Yes ☐ No ☐

HIV Status Positive ☐ Negative ☐

Smoking History Yes ☐ No ☐

Year of initiation on dialysis:

Comorbidities	Yes	No
Diabetes Mellitus		
Hypertension		
Dyslipidaemia		

Duration on Peritoneal Dialysis:

Duration on Haemodialysis:

<u>Clincal Data</u>

Previous CVS events	Yes	No
Myocardial infarction		
CerebrovascularAccident		

Systolic blood pressure:

Diastolic blood pressure:

Pulse rate:

Dry Weight:

Height:

Dialysis access (if on HD):

Antihypertensive drugs	Yes	No
Loop diuretic		
ACE - inhibitor		
>5 AntiHPT agents		

Laboratory Parameter	Result
Parathyroid hormone(ng/l)	
Calcium(mmol/l)	
Phosphate(mmol/l)	
Uric Acid(mmol/l)	
HbA1c(%)	
Triglyceride (mmol/l)	
Total cholesterol(mmol/l)	
HDL-C(mmol/l)	
LDL-C(mmol/l)	
Alkaline Phosphatase(U/l)	
Haemoglobin(g/dl):	
Ferritin (mcg/l)	
Transferrin saturation(%)	
Sodium (mmol/l)	
Potassium(mmol/l)	
Albumin(g/dl)	
Random glucose (mmol/l)	
Urea (mmol/l)	
Creatinine (umol/l)	

Hypoglycaemic Drugs	Yes	No
Insulin		

Secondary prevention	Yes	No
Aspirin		
Statin		

Phosphate binders and Vitamins	Yes	No
Calcium carbonate		
Cholecalciferol		

Haematopoeitic agents	Yes	No
Iron (IV and Oral)		
Erythropoeitin(EPO)		
Weekly dose of EPO		

Appendix C: Protocol Assessors Meeting Outcome

University of the Witwatersrand

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG
FACULTY OF HEALTH SCIENCES
ASSESSORS MEETING

CANDIDATE: Jose Jacob (Student No: 0701877X)

Date of Assessor Group Meeting: Wednesday, 13 June 2018 School / Department / Division: INTERNAL MEDICINE

Yes / No Is the research question clearly identified and described?

Comments:

Yes / No / Not entirely

Is the design of the study and methods the methods used appropriate for the research question being asked?

Comments:

Expand on references used
Mention HIV/n non-traditional risk factors
Change the objective order: make objective 3 into 1
Page 3: Burden of CKD (further info required re: %)

Is it possible to make substantial improvements based on study findings

Is the study feasible within:

i. the applicant's resources? Yes / No
ii. the departments resources? Yes / No
iii. the time frame? Yes / No

Do you recommend:

i. Shortening / lengthening of the protocol? Please specify and explain.

_____

_____

_____

ii. The appointment of a co-supervisor? Yes [ ] No [✓]

Nominee/s : _____

_____

Overall recommendation regarding the protocol :

i. revision of the protocol to the Supervisor / Head of Department: (**Candidates**: one copy, list of corrections, supervisor approval letter – submit to PG Office) Yes [✓] No [ ]

ii. revision of the protocol to the satisfaction of the Assessor Group: (**Candidates**: six copies, list of corrections, supervisor approval letter – submit to PG Office) Yes [ ] No [ ]

iii. revision of the protocol and resubmission of the revised protocol to the next Assessor Group Meeting: (**Candidates**: six copies, list of corrections, supervisor approval letter – submit one copy to PG Office / 5 to school assessor group administrator) Yes [ ] No [ ]

iv. candidate goes ahead: Yes [✓] No [ ]

Assessor Names and Signatures :

Dr K Hari _____

Dr. A. Lai _____

Dr. A. Peter _____

Date: Wednesday, 13 June 2018

Jose Jacob (Student No: 0701877X)

Appendix D: Ethics Clearance Certificate

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

R14/49 Dr J Jacob

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)
CLEARANCE CERTIFICATE NO. M200160

NAME: (Principal Investigator)	Dr J Jacob
DEPARTMENT:	School of Clinical Medicine Department of Medicine Division of Internal Medicine Medical School University
PROJECT TITLE:	Traditional and non-traditional cardiovascular risk factors in the chronic dialysis population at Chris Hani Baragwanath Academic Hospital and Sebokeng Provincial Hospital
DATE CONSIDERED:	2020/01/31
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Drs G Teckie and NG Mahyoodeen
APPROVED BY:	CB Penny Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	2020/06/29

This clearance certificate is valid for 5 years from the date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the 3rd Floor, Phillip Tobias Building, Parktown, University of the Witwatersrand, Johannesburg.
I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions. Should any departure be contemplated, from the research protocol as approved, I/we undertake to submit details to the Committee. **I agree to submit a yearly progress report**. When a funder requires annual re-certification, the application date will be one year after the date when the study was initially reviewed. In this case, the study was initially reviewed in **January** and will therefore reports and re-certification will be due early in the month of **January** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature _____ Date _____

Appendix E: Turn-It In Report

Dr J Jacob MMED 28:3:2025-1.docx

ORIGINALITY REPORT

27%	19%	23%	5%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	www.science.gov Internet Source	1%
2	Submitted to University of Witwatersrand Student Paper	1%
3	www.journals.ac.za Internet Source	1%
4	archive.org Internet Source	1%
5	Tatsuya Suwabe, Yoshifumi Ubara, Yuki Oba, Hiroki Mizuno et al. "Changes in Kidney and Liver Volumes in Patients With Autosomal Dominant Polycystic Kidney Disease Before and After Dialysis Initiation", Mayo Clinic Proceedings: Innovations, Quality & Outcomes, 2023 Publication	1%
6	www.termedia.pl Internet Source	1%
7	"Pediatric Dialysis", Springer Science and Business Media LLC, 2021 Publication	1%
8	David Roseveare. "World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCO-IOF-ESCEO 2018): Poster Abstracts", Osteoporosis International, 2018 Publication	1%

9	academic.oup.com Internet Source	1 %
10	pubmed.ncbi.nlm.nih.gov Internet Source	1 %
11	www.revistanefrologia.com Internet Source	<1 %
12	journals.plos.org Internet Source	<1 %
13	D. A Lawlor. "Sex differences in body fat distribution and carotid intima media thickness: cross sectional survey using data from the British regional heart study", Journal of Epidemiology & Community Health, 2004 Publication	<1 %
14	Ivana Mikolasevic, Marta Žutelija, Vojko Mavrinac, Lidija Orlic. "Dyslipidemia in patients with chronic kidney disease: etiology and management", International Journal of Nephrology and Renovascular Disease, 2017 Publication	<1 %
15	"Nephrology Worldwide", Springer Science and Business Media LLC, 2021 Publication	<1 %
16	Giuseppe Mancia, Guido Grassi, Konstantinos P. Tsioufis, Anna F. Dominiczak, Enrico Agabiti Rosei. "Manual of Hypertension of the European Society of Hypertension", CRC Press, 2019 Publication	<1 %
17	Hsu, Hon-Chun. "Cardiovascular Disease and its Associated Risk Factors in South African Chronic Kidney Disease Patients", University	<1 %

	of the Witwatersrand, Johannesburg (South Africa), 2025 Publication	
18	bmcnephrol.biomedcentral.com Internet Source	<1 %
19	Drukker, Parsons, Maher. "Replacement of Renal Function by Dialysis", Springer Nature, 2004 Publication	<1 %
20	etheses.bham.ac.uk Internet Source	<1 %
21	www.kjfm.or.kr Internet Source	<1 %
22	Becker, Anthony Charles. "Acute Coronary Syndromes in Black South African Patients with Human Immunodeficiency Virus Infection", University of the Witwatersrand, Johannesburg (South Africa), 2025 Publication	<1 %
23	mts.intechopen.com Internet Source	<1 %
24	www.portailvasculaire.fr Internet Source	<1 %
25	c.coek.info Internet Source	<1 %
26	repositorio.unifesp.br Internet Source	<1 %
27	wiredspace.wits.ac.za Internet Source	<1 %
28	James B Young. "Pretransplant cardiovascular evaluation and posttransplant cardiovascular risk", Kidney International, 09/2010	<1 %

	Publication	
29	Neelu Mathew, Malcolm Davies, Feroza Kaldine, Zaheera Cassimjee. "Comparison of Quality of Life in patients with advanced chronic kidney disease undergoing haemodialysis, peritoneal dialysis and conservative management in Johannesburg, South Africa: a cross-sectional, descriptive study", Research Square Platform LLC, 2022 Publication	<1 %
30	"Cardio-Nephrology", Springer Science and Business Media LLC, 2017 Publication	<1 %
31	Jerotić, Đurđa D.. "Association of NRF2, SOD2 and GPX1 Gene Polymorphisms with Markers of Oxidative Stress and Prognosis in Patients with end Stage Renal Disease", University of Belgrade (Serbia), 2024 Publication	<1 %
32	dx.doi.org Internet Source	<1 %
33	"ASPC Manual of Preventive Cardiology", Springer Science and Business Media LLC, 2021 Publication	<1 %
34	"UEG Week 2018 Poster Presentations", United European Gastroenterology Journal, 2018 Publication	<1 %
35	Lian Feenstra, Melanie Reijrink, Andreas Pasch, Edward R Smith et al. "Calciprotein particle counts associate with vascular remodelling in chronic kidney disease", Cardiovascular Research, 2024 Publication	<1 %

36	Mudi, Abdullahi. "Cardiovasular Risk Factors and Their Association With Biomarkers in Children With Chronic Kidney Disease in Johannesburg, South Africa", University of the Witwatersrand, Johannesburg (South Africa), 2025 Publication	<1 %
37	Nalado, Aishatu Muhammad. "Functional Iron Deficiency Anaemia and Its Genetics in a Black South African Population with Chronic Kidney Disease", University of the Witwatersrand, Johannesburg (South Africa), 2025 Publication	<1 %
38	annalsafrmed.org Internet Source	<1 %
39	link.springer.com Internet Source	<1 %
40	Brian J Pollard, Gareth Kitchen. "Handbook of Clinical Anaesthesia", Routledge, 2017 Publication	<1 %
41	Magda Fliszkiewicz, Mariusz Niemczyk, Andrzej Kulesza, Anna Łabuś, Leszek Pączek. "Glucose and Lipid Metabolism Abnormalities among Patients with Autosomal Dominant Polycystic Kidney Disease", Kidney and Blood Pressure Research, 2019 Publication	<1 %
42	Qiang Yao, Roberto Pecoits-Filho, Bengt Lindholm, Peter Stenvinkel. "Traditional and non-traditional risk factors as contributors to atherosclerotic cardiovascular disease in end-stage renal disease", Scandinavian Journal of Urology and Nephrology, 2009 Publication	<1 %

52	Internet Source	<1 %
53	jcmsa.org.za Internet Source	<1 %
54	www.msjonline.org Internet Source	<1 %
55	Jinxi Li, Ting Xiang, Xinyun Chen, Ping Fu. "Neutrophil-percentage-to-albumin ratio is associated with chronic kidney disease: Evidence from NHANES 2009–2018", PLOS ONE, 2024 Publication	<1 %
56	Nang-yue Kuang, Ye Hong, Jie-ping Chen, Hui Li, Na Tang. "Risk factors for fasting blood glucose control in middle-aged and elderly type 2 diabetes patients", Medicine, 2024 Publication	<1 %
57	Seon Ha Baek, Kook-Hwan Oh, Sejoong Kim, Dong Ki Kim et al. "Control of fluid balance guided by body composition monitoring in patients on peritoneal dialysis (COMPASS): study protocol for a randomized controlled trial", Trials, 2014 Publication	<1 %
58	bmccardiovascdisord.biomedcentral.com Internet Source	<1 %
59	karger.com Internet Source	<1 %
60	qspace.library.queensu.ca Internet Source	<1 %
61	www.renal.org Internet Source	<1 %

62	www.xjcistanche.com Internet Source	<1 %
63	www.yumpu.com Internet Source	<1 %
64	Amira, Christiana Oluwatoyin. "Risk Factors for Atherosclerosis in Black South African Patients on Haemodialysis", University of the Witwatersrand, Johannesburg (South Africa), 2025 Publication	<1 %
65	Chia-Ter Chao, Min-Tser Liao, Chung-Kuan Wu. "Combinations of valvular calcification and serum alkaline phosphatase predict cardiovascular risk among end-stage kidney disease patients", IJC Heart & Vasculature, 2024 Publication	<1 %
66	Ha, Jeffrey Tsun Kit. "Cardiovascular Risk in Chronic Kidney Disease.", University of New South Wales (Australia) Publication	<1 %
67	K.M., Rashmi. "Pharmacotherapy of Chronic Kidney Disease and Determinants of Short-Term Outcomes in a Tertiary- Care Hospital", Rajiv Gandhi University of Health Sciences (India), 2023 Publication	<1 %
68	Mbhele, Thapelo. "The Determination of Early Potential Biomarkers for Diabetic Nephropathy in Human Urine Samples Using Ultra High-Performance Liquid Chromatography Coupled to Quadrupole Time of Flight High Resolution Mass Spectrometer (UHPLC - QTOF HRMS)",	<1 %

	University of the Witwatersrand, Johannesburg (South Africa), 2025 Publication	
69	Nkosingiphile Twala, Grace Tade, Patrick Dessein, Gloria Teckie. "Causes of Chronic Kidney Disease and Their Associations with Cardiovascular Risk and Disease in a Sub-Saharan Low-Income Population", International Journal of Nephrology and Renovascular Disease, 2024 Publication	<1 %
70	Sari Mishina, Miina Waratani, Satoshi Onozawa, Hiroyuki Okumura, Yuichiro Ito, Yoshinari Yasuda. "A retrospective database analysis of erythropoiesis-stimulating agent treatment patterns and associated healthcare resource use in patients with non–dialysis-dependent chronic kidney disease–related anaemia in Japan", Nephrology, 2023 Publication	<1 %
71	ia601009.us.archive.org Internet Source	<1 %
72	issuu.com Internet Source	<1 %
73	jamanetwork.com Internet Source	<1 %
74	lopbeirut.org Internet Source	<1 %
75	mdpi-res.com Internet Source	<1 %
76	portal.findresearcher.sdu.dk Internet Source	<1 %
	repub.eur.nl	

77	Internet Source	<1 %
78	unsworks.unsw.edu.au Internet Source	<1 %
79	www.frontiersin.org Internet Source	<1 %
80	www.kdigo.org Internet Source	<1 %
81	www.mdpi.com Internet Source	<1 %
82	www.rxfiles.ca Internet Source	<1 %
83	www.sjkdt.org Internet Source	<1 %
84	www.tandfonline.com Internet Source	<1 %

Exclude quotes	On	Exclude matches	< 8 words
Exclude bibliography	On		