A RETROSPECTIVE STUDY TO DETERMINE THE PREVALENCE AND DEGREE OF HYPERKALAEMIA IN ADULT PATIENTS WITH CHRONIC KIDNEY DISEASE, ATTENDING THE RENAL CLINIC AT INKOSI ALBERT LUTHULI CENTRAL HOSPITAL.

BY DR TASNEEM BUX

217080529

Submitted in partial fulfillment of the academic requirements for the degree of Master of Medicine

Department of Internal Medicine

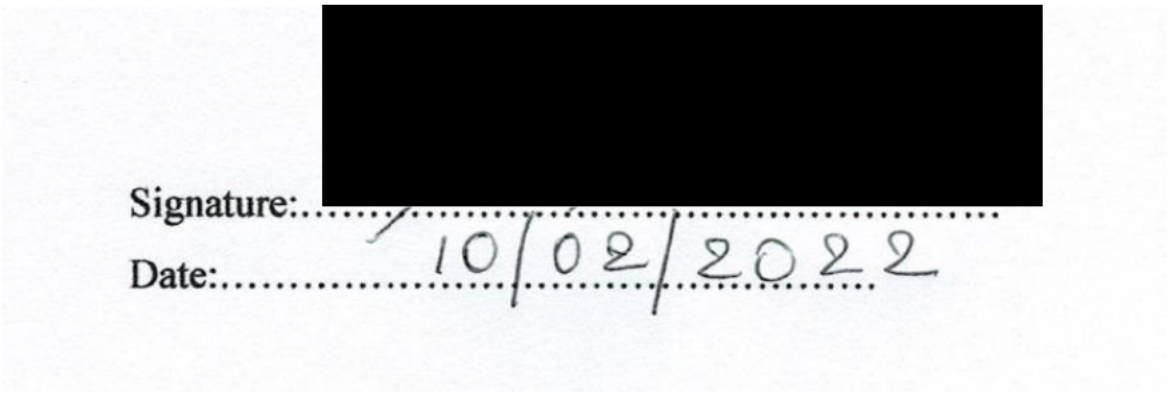
School of Clinical Medicine

College of Health Sciences

University of KwaZulu – Natal

Supervisor: Prof A. Assounga

As the candidate's supervisor I have approved this thesis for submission:



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Dedication

To my husband Aslam, for his love and unwavering support.

To my friends Jonathan and Astley, who have helped me in immeasurable ways throughout the last few years.

Acknowledgements

I would like to express my gratitude to Professor Assounga for his support throughout this study.

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List of Abbreviations

ACE – Angiotensin converting enzyme

ACEI – Angiotensin converting enzyme inhibitor

ARB – Angiotensin II receptor blocker

ART – Antiretroviral therapy

CAD – Coronary Artery Disease

CAPD – Continuous Ambulatory Peritoneal Dialysis

CI – Confidence interval

CKD – Chronic kidney disease

CVD – Cardiovascular disease

DM – Diabetes mellitus

eGFR – estimated glomerular filtration rate

ESRD – End stage renal disease

GSH – General Household Survey

HD – Haemodialysis

Hep B – Hepatitis B virus

Hep C – Hepatitis C virus

HIV – Human immunodeficiency virus

HT – Hypertension

IALCH – Inkosi Albert Luthuli Central Hospital

K^+ - Potassium

KDIGO – Kidney Disease: Improving Global Outcomes

KRT – Kidney replacement therapy

KZN – KwaZulu - Natal

MRA – Mineralocorticoid receptor antagonist

PD – Peritoneal dialysis

RA – Rheumatoid arthritis

RAAS - Renin Angiotensin Aldosterone System

ROMK channel – Renal outer medullary potassium channel

SA – South Africa

SLE – Systemic lupus erythematosus

SPS – Sodium Polystyrene Sulfonate

SSA – Sub-Saharan Africa

U-ACR – Urine albumin:creatinine ratio

VL – Viral load

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Chapter 1: Abstract

Background: The presence of hyperkalaemia is a known risk factor for the development of cardiac rhythm disturbances and sudden cardiac death. The presence of chronic kidney disease (CKD) is also an independent risk factor for cardiovascular complications. The prevalence of hyperkalaemia in patients with CKD has previously varied widely between studies. The prevalence of hyperkalaemia in the patients attending the renal clinic at Inkosi Albert Luthuli Central Hospital (IALCH) has not been previously determined.

Objectives: This study aimed to discover the prevalence of hyperkalaemia in patients attending the renal clinic at IALCH, as well as the degree of severity amongst the patients in whom hyperkalaemia was present. Demographic and other variables were also assessed for an association with hyperkalaemia.

Methods: A retrospective review of outpatients attending the renal clinic at IALCH from 1 October 2016 until 30 September 2017.

Results: The study consisted of 200 patients, of whom the majority were female (n=120, 60%). The prevalence of hyperkalaemia amongst these patients was found to be 16%. In those with stage 3 CKD, the prevalence of hyperkalaemia was 7.69%. In those with stage 4 CKD, the prevalence of hyperkalaemia was 20.5% and in those with stage 5 CKD the prevalence was 17.3%. There were no statistically significant associations between hyperkalaemia and demographic variables, nor with dietician intervention. There was a significant association with the use of sodium polystyrene sulfonate.

Conclusion: CKD is a growing burden in the developing world. With CKD comes metabolic and other derangements, including electrolyte abnormalities as well as increased cardiovascular risk. Hyperkalaemia is associated with worsening CKD. In addition, hyperkalaemia puts patients at risk of cardiac dysrhythmias and sudden cardiac death. Pharmacological measures to manage CVD risk should be weighed up against the risk of hyperkalaemia related complications. Potassium lowering agents should be considered in order to allow for optimal CVD management in the setting of hyperkalaemia in CKD.

Chapter 2:

Introduction and Background

Chronic kidney disease (CKD) is a growing health problem throughout the world. The prevalence varies throughout, but specific studies relating to the South African setting are lacking. The prevalence of CKD in South Africa (SA), as well as sub-Saharan Africa (SSA), varies widely based on the limited available studies. One systemic review and meta-analysis of 98 African studies involving close to 100 000 participants showed the overall prevalence to be 15.8% for CKD stages 1 to 5. (1)

One thing that cannot be escaped is that this condition is increasingly becoming a burden, with resultant increasing costs for the healthcare sector. An additional factor of concern is the paucity of suitably trained nephrology staff within South Africa, as well as the discrepancy between the availability of adequately trained staff within the private versus public healthcare sector.(2) The public sector also faces the additional challenges relating to care of patients with CKD, such as a paucity of specialized nephrology centers, limited availability of dialysis and the fact that it caters to much of the South African population, who cannot afford private health insurance. Hassen and colleagues identified a total of 120 adult nephrologists in South Africa. The bulk of them were situated in 3 of the 9 provinces in SA, with 2 provinces having no nephrologist at all. The majority were also concentrated within the private sector, which serves less than 20% of the population. In addition to this, 2 provinces have no public sector dialysis centers. (2)

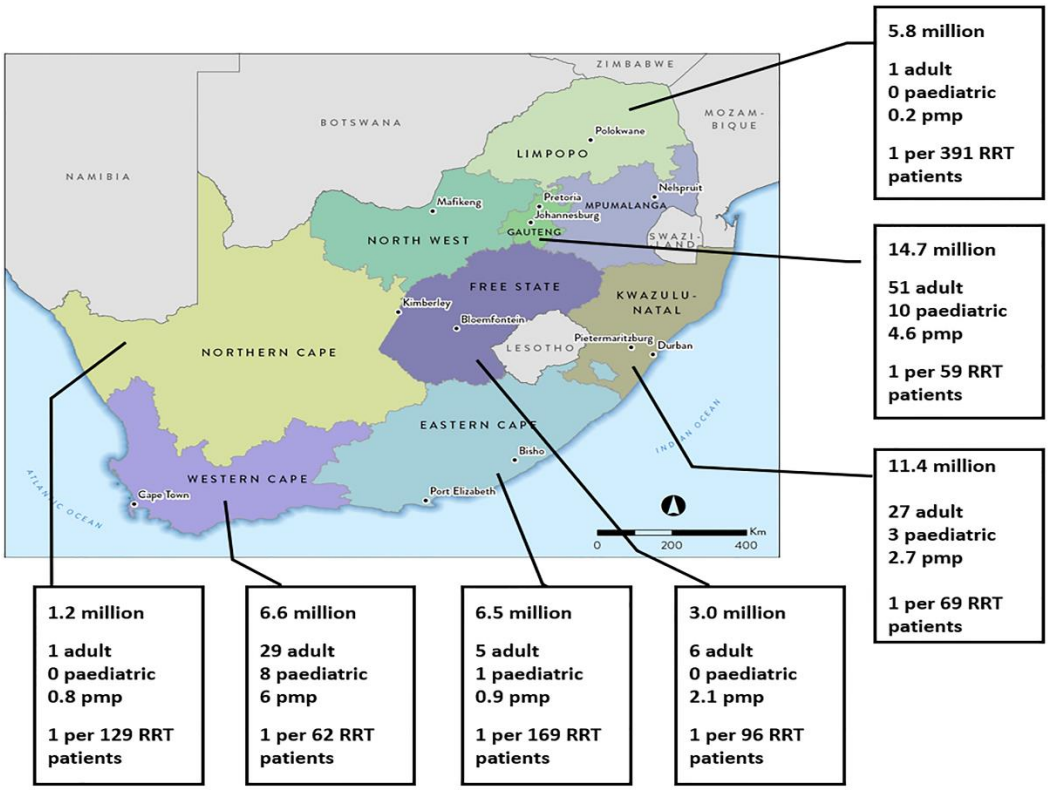


Figure 1:

Distribution and density of nephrologists in South Africa. The data panel for each province lists, in order, population of the province in millions, number of adult nephrologists, number of paediatric nephrologists, nephrologist density (per million population) and ratio of nephrologists to patients on renal replacement therapy. Abbreviations: pmp, per million population; RRT, renal replacement therapy. Doi: https://doi.org/10.1371/journal.pone.0228890.g001

There are many factors which contribute to the development of CKD, including several non - communicable diseases which are becoming increasingly prevalent in the modern world. These include conditions such as hypertension, diabetes mellitus and obesity. (3,4) These conditions contribute particularly to cardiovascular morbidity and mortality. CKD has been found to be an independent risk factor for cardiovascular disease, further compounding this issue. (5) In our South African setting, the role of communicable infectious diseases such as human immunodeficiency virus (HIV) also plays a significant role. (6) Trauma and pregnancy related complications, though not communicable infectious diseases, also play a role in the burden of both acute and CKD in the South African setting. (7,8)

There are numerous complications of CKD, of which electrolyte abnormalities feature prominently, especially in end stage renal disease (ESRD). Hyperkalaemia is one of these electrolyte abnormalities. (9,10,11) The increase in potassium levels is related to decreased

excretion in CKD, and may be further influenced by diet, medications used to control the progression of CKD as well as medications used to treat comorbid conditions in those with CKD. (10,11) An understanding of normal potassium homeostasis is important to further understand the contribution of these factors. (12)

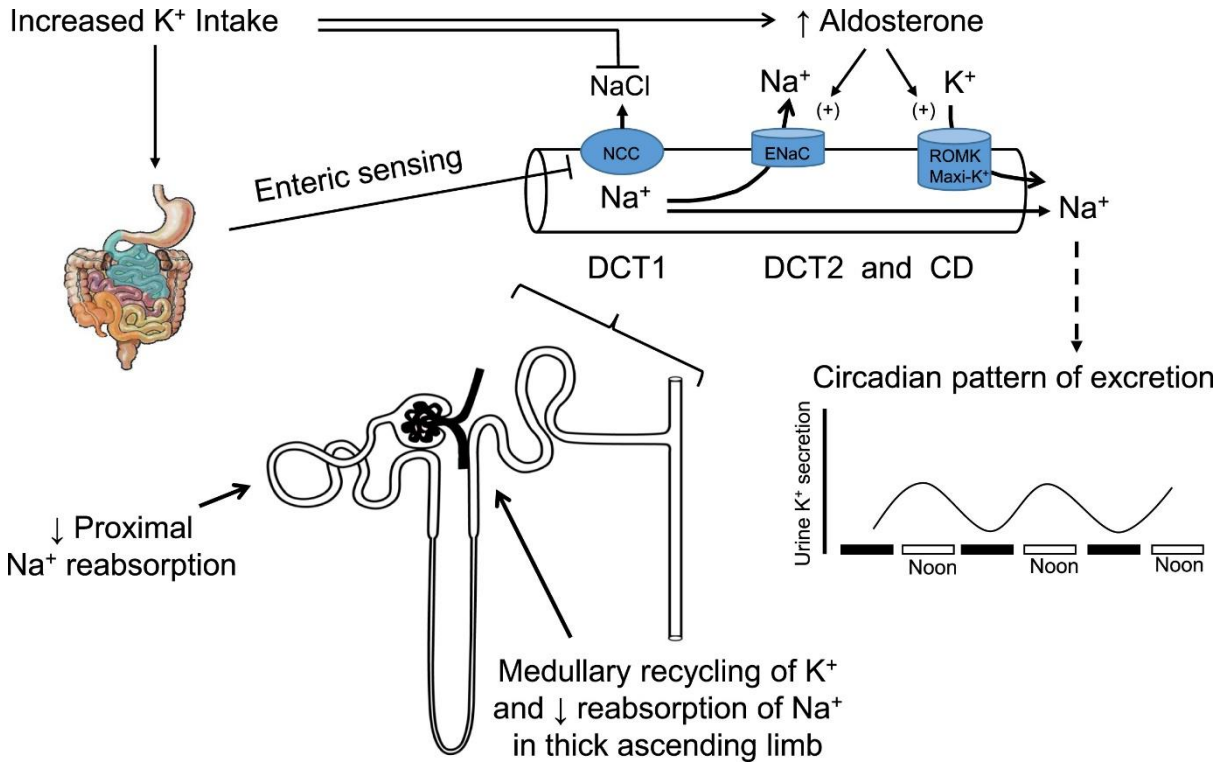


Figure 2

Representation of mechanisms to achieve potassium homeostasis in the kidney, including enteric potassium sensing mechanisms, urinary potassium secretion and the circadian rhythm of ROMK channels.

American Journal of Kidney Diseases 2019 74682-695DOI: (10.1053/j.ajkd.2019.03.427)

The kidney has several mechanisms to deal with electrolyte, and potassium, shifts. The distal convoluted tubule (DCT) has the capacity to augment potassium secretion in response to small changes in serum potassium concentration. Enteric potassium sensing mechanisms trigger potassium secretion when potassium enters the gastrointestinal (GI) tract. There is urinary potassium secretion, and secretion follows a circadian rhythm with levels of renal outer medullary potassium (ROMK) channels increased during daylight hours and with activity. (12,13)

With the rise of CKD, and with HT as a known cause of CKD, potassium level as it relates to BP has been studied in some centers. (14) Potassium has been recognized as having a role in

determining levels of blood pressure, and interestingly those who increased their dietary intake of potassium have been described to have lowered their blood pressures, with the decrease in BP being more significant in black patients than white. Previously, lower urinary excretion of potassium in black patients was thought to be due to their lower dietary potassium intake, however these differing levels may not actually reflect dietary differences. (14,15) Differing comorbid conditions as well as the use of differing medications may also have a role to play. Using 2 large diverse cohorts, Chen et al., found that potassium levels were on average lower, in Americans of African descent than those of European decent. (16)

Higher rates of hyperkalaemia are observed in those with CKD, as opposed to the general population. (17) Despite the knowledge that prevalence rates are higher in CKD, the exact prevalence of hyperkalaemia is not known. Humphrey et al had an "objective to provide a comprehensive overview of the epidemiology of hyperkalaemia within the general population, across different continents and in different healthcare settings". In this systematic review and meta-analysis of the prevalence and incidence of hyperkalaemia, they included 542 articles from a total of over 14 000 articles. Embase and Medline were searched from database inception until February 2021 for the abovementioned articles. The prevalence of hyperkalaemia from their work, by any definition and across all adult studies was found to be 6.3% (95% confidence interval: 5.8%-6.8%). Hyperkalaemia, by any definition, was found to be highest amongst patients with known kidney injury; specifically acute kidney injury (24.8%), renal transplant patients (21.8%) and those with end stage renal disease (21.5%). (18)

An Italian study by Maggioni et al in 2021 showed the prevalence of hyerkalaemia in the general population to be 0.035%. In patients with heart failure, the prevalence of hyperkalaemia was found to be two orders of magnitude greater than amongst the general population at 3.6 to 4.3%. The presence of hyperkalaemia was interestingly found to be associated with underuse of renin-angiotensin-aldosterone system blocking agents. CKD was amongst the most frequent comorbidities in these patients.(19)

There are some studies that suggest that both hyperkalaemia and hypokalaemia are independently associated with poorer outcomes in patients with CKD not receiving kidney replacement therapy (KRT). (17) Interestingly, limited evidence suggests there may be a link between hypokalaemia and progression of CKD. (20) Mild levels of hyperkalaemia are often asymptomatic, but higher levels of potassium are known to cause cardiac disturbances and arrhythmias. (21,22) It appears that patients with chronic hyperkalaemia may be asymptomatic at higher levels, but that rapid changes in potassium level may precipitate symptoms at lower levels. (22,23)

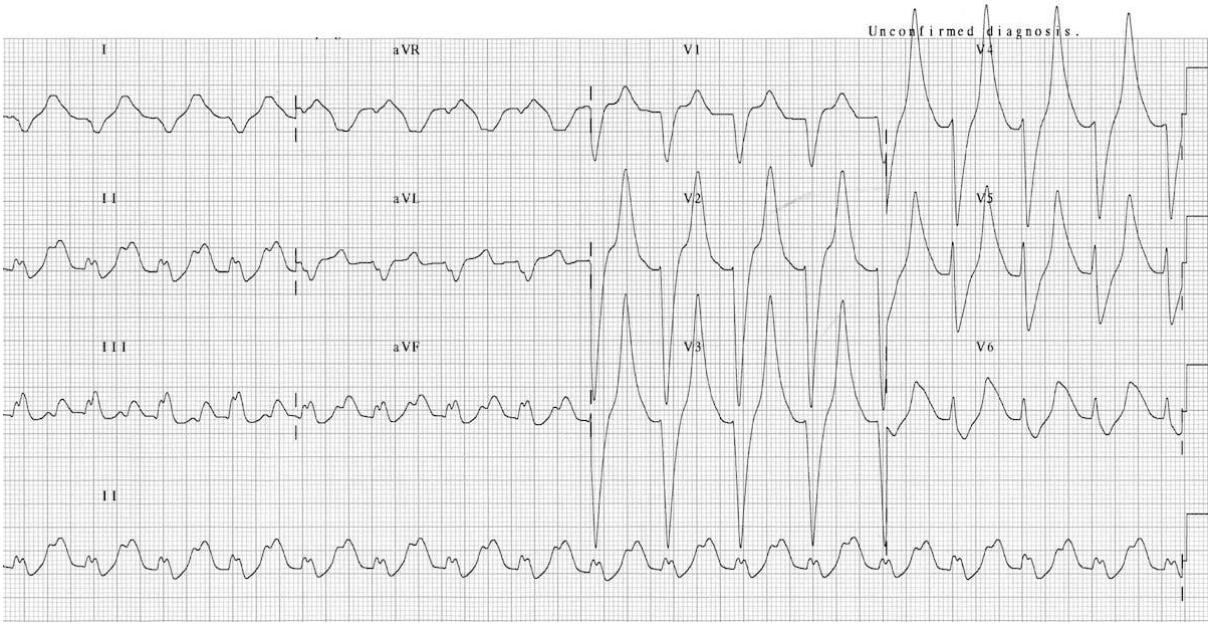


Figure 3: An electrocardiogram showing P wave prolongation and peaked T waves in a patient with hyperkalaemia

https://litfl.com/wp-content/uploads/2018/08/ECG-Hyperkalemia-serum-potassium-9.3.jpg

The prevalence of hyperkalaemia in the patient population attending the renal clinic at IALCH will be determined in this study. Confounding factors and associations will also be investigated.

Literature Review and Motivation

Chronic kidney disease has been increasingly recognised as a global health problem. It has also been recognized as an independent risk factor for cardiovascular disease. CKD results in morbidity, mortality, and decreased quality of life. (1) The prevalence of CKD has been reported with variability worldwide, but information on the South African setting is limited. (2)

CKD may be defined as (3):

Kidney damage or glomerular filtration rate (GFR) <60mL/min/1.73m^2 for at least 3 months, irrespective of cause.

More specifically, Kidney Disease: Improving Global Outcomes (KDIGO) classifies the stages of CKD as follows:

Stage	GFR (ml/min/1.73m^2)	Terms
1	≥90	Normal or high
2	60-89	Mildly decreased
3a	45-59	Mildly to moderately decreased
3b	30-44	Moderately to severed decreased
4	15-29	Severely decreased
5	<15	Kidney failure

Figure 4: KDIGO classification of CKD from stage 1 to 5

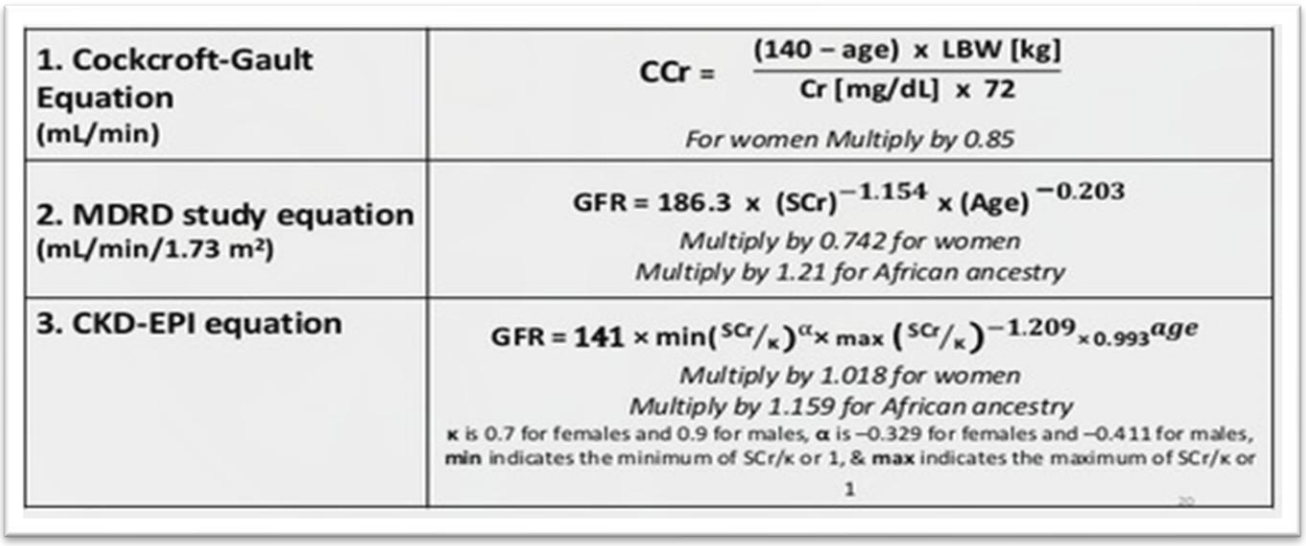
https://www.researchgate.net/figure/KDIGO-classification-of-the-stages-of-chronic-kidney-disease_tbl2_290532511

The KDIGO criteria include stage 1 and 2 CKD; these patients are more difficult to identify as they have an eGFR of above 60, although they already have structural changes to the kidney itself which can progress to stage 3 and beyond. (3) This is an important group of patients to identify to prevent the progression of CKD. In many diabetic clinics, patients have their urine tested for the albumin: creatinine ratio at all visits. This is important to identify patients with microalbuminuria who will benefit from early intervention to prevent the progression to CKD.

GFR and creatinine clearance may be estimated by several equations. (3,4)

In our study setting, the Modified Diet in Renal Disease (MDRD) equation is used to calculate estimated GFR in patients. Other calculations are the Cockcroft Gault equation, and the Chronic

Kidney Disease Epidemiology Collaboration (CKD-EPI). The latter was developed to have a more accurate calculation of eGFR based on serum creatinine as well as other clinical parameters. (4) The MDRD and CKD-EPI equations include variables for age, gender, race; this can allow for a better estimation of GFR where the serum creatinine appears to be within normal parameters.



1. Cockcroft-Gault Equation (mL/min)	$CCr = \frac{(140 - age) \times LBW\ [kg]}{Cr\ [mg/dL] \times 72}$ *For women Multiply by 0.85*
2. MDRD study equation (mL/min/1.73 m²)	$GFR = 186.3 \times (SCr)^{-1.154} \times (Age)^{-0.203}$ *Multiply by 0.742 for women* *Multiply by 1.21 for African ancestry*
3. CKD-EPI equation	$GFR = 141 \times \min(SCr/\kappa)^{\alpha} \times \max(SCr/\kappa)^{-1.209} \times 0.993^{age}$ *Multiply by 1.018 for women* *Multiply by 1.159 for African ancestry* **κ** is 0.7 for females and 0.9 for males, **α** is −0.329 for females and −0.411 for males, **min** indicates the minimum of SCr/κ or 1, & **max** indicates the maximum of SCr/κ or 1

Figure 5: Equations for estimation of GFR

https://fadic.net/creatinine-clearance-calculator/

There are numerous complications of CKD, which include but are not limited to anaemia, acidosis and electrolyte abnormalities. (5,6,7)

Hyperkalaemia is an electrolyte abnormality often noted as CKD stage progresses. Hyperkalaemia is associated with cardiac arrhythmias, and there is a risk of sudden cardiac death in severe cases. (8) Causes of hyperkalaemia are varied, but of particular importance in the setting of impaired renal function.

Potassium is critical for maintaining normal cellular function. Majority of the body potassium stores are found within the cell, with a small amount (2%) being extracellular. Cells are equipped with a Na^+K^+ ATPase, which produces a potassium gradient across the cell membrane by pushing sodium out in exchange for potassium. This is partially responsible for the maintenance of membrane potential of the cells, especially important in excitable cells which rely on this gradient for normal function. (8,9) Renal handling of this potassium balance is of particular importance, especially as relates to increasing potassium levels as renal function deteriorates. Potassium is freely filtered across the glomerulus. It is then extensively reabsorbed across the proximal convoluted tubule, where solute drag plays a key role in this reabsorption. (10) Dietary intake of potassium rarely contributes to hyperkalaemia in people with normal kidney function. In addition,

not all potassium containing or enriched foods, produce the same sustained changes in serum potassium concentration. (11) Insulin release following a meal not only regulates glucose concentration but also plays a role in shifting dietary potassium into cells. Catecholamines also have a role in maintaining potassium homeostasis. (11,12,13)

The exact definition of hyperkalaemia is varied in the literature (14,15). Some refer to hyperkalaemia as being a potassium level which is above the upper limit of what is considered normal by the reporting laboratory reference range. Other literature refers to hyperkalaemia as a potassium level greater than or equal to 5.5 mmol/L (15,16). Hyperkalaemia may further be defined as:

- Mild – 5.5mmol/L to 5.9mmol/L
- Moderate – 6mmol/L to 6.5mmol/L
- Severe - >6.5mmol/L

The above-mentioned definition will be used in this study. (15,16)

Identifying those patients with hyperkalaemia will allow for noting those at increased risk of cardiac morbidity and mortality. Identifying these patients will also allow for implementation of strategies and treatment aimed at controlling hyperkalaemia. Identifying the characteristics of those patients more likely to present with hyperkalaemia will also assist in earlier identification and treatment of these patients, possibly prior to the first event.

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Chapter 3: Methods

Title of the Study:

A retrospective study to determine the prevalence and degree of hyperkalaemia in adult patients with CKD, attending the renal clinic at IALCH.

Aim of Study:

To determine the prevalence and degree of hyperkalaemia in adult patients with CKD, attending the renal clinic at IALCH, and to determine the role, if any, that variable demographic parameters and comorbidities had on this prevalence.

Specific objectives:

1. To determine the prevalence of hyperkalaemia in patients with CKD attending the renal clinic at IALCH.
2. To determine the degree of hyperkalaemia of each patient according to the stage of CKD.
3. To determine the difference in prevalence of hyperkalaemia between those with CKD not on KRT, and those undergoing peritoneal dialysis (PD) and/or haemodialysis (HD).
4. To assess the association of variables such as age, gender, ethnicity, stage of CKD and comorbidities that may have had an impact on the prevalence of hyperkalaemia within this group of patients.

Study Design:

Study Population:

The study population comprised 200 patients with CKD including those not yet receiving KRT as well as patients with ESRD undergoing PD and patients with ESRD undergoing HD at IALCH, who were attending the renal clinic at IALCH and were assessed both clinically and biochemically within the study period.

Sampling strategy and statistical planning and analysis:

This is a retrospective, descriptive study.

A minimum of 200 patients seen consecutively during the study period were selected.

There were 2022 distinct patients that visited the Renal Clinic at IALCH between October 2016 and September 2017.

Inclusion Criteria:

This study includes patients 18 years and older, attending the renal clinic at IALCH with a diagnosis of CKD, between 1 October 2016 and 30 September 2017.

Exclusion Criteria:

This study excludes patients younger than 18 years of age.

Data collection methods and Tools:

The data collection period fell between 1 October 2016 and 30 September 2017.

A list of patients was generated from a computerised data mining system. Once this had occurred, consecutive files were selected and reviewed until a minimum number of 200 was reached.

Information relating to the patients' age, gender, ethnicity and comorbidities was collected from the information recorded as computerised data on the hospital system at IALCH.

Blood results relating to each visit were collected from the information recorded as computerised data on the hospital system at IALCH.

The data was captured and subsequently analysed using the IBM SPSS (Statistical Packages for Social Sciences) Statistics V28 and the statistical tools used were descriptive, correlation and regression statistics. Means/medians were used to describe the continuous variables whilst categorical variables were described with counts and proportions (%). Simple logistic regression was used to assess the relationship between potassium (dependent variable) and other demographic and clinical variables. To determine the effect of other variables on the dependent variable, odd's ratios, 95% confidence interval and *p* values (value <0.05 taken as significant) were estimated for each variable.

Study Location:

Inkosi Albert Luthuli Central Hospital.

This is quaternary medical institution in the city of Durban, in KwaZulu Natal. This academic institution serves as a referral centre for regional and district hospitals across this province, as well as a portion of Eastern Cape. The Department of Nephrology located at this facility serves as the main referral centre for both peritoneal and haemodialysis in the province, although, to facilitate access to these services, satellite sites have been set up in other hospitals throughout the province.

Study Period:

1 October 2016 to 30 September 2017.

Limitations to the study:

This study only included patients with chronic kidney disease attending the renal clinic at IALCH, which is a quaternary level public sector hospital. Consequently, the proportion of patients with advanced stages of chronic kidney disease was expected to be higher. The sample would not be representative of those with CKD who were not yet referred, or who demised before they could be assessed for KRT.

This study only included patients 18 years or older, however those as young as 12 years of age are sometimes referred to adult centres.

This study was retrospective and not longitudinal. Only one visit per patient was reviewed.

Ethical considerations:

This was a descriptive, retrospective study. However, all patient data was deidentified and patient confidentiality maintained. Ethical approval was sought from BREC (BE019/18).

Chapter 4: Results

Table 1: Demographic and Clinical Characteristics of Study Sample

	Total	Male	Female
Gender *n*(%)	200 (100)	80 (40)	120 (60)
Age in years (Median)	51	45	53
Standard deviation	±13.42	±19.8	±16.8
Range		18 – 76	18-84
Race *n*(%)			
Black	111 (55.5)	43 (21.5)	68 (34)
Indian	82 (41)	33 (16.5)	49 (24.5)
White	4 (2)	2 (1)	2 (1)
Coloured	2 (1)	1 (0.5)	1 (0.5)
Unknown	1 (0.5)	1 (0.5)	0
Comorbidities *n*(%)			
Hypertension	161 (80.5)	66 (33)	95 (47.5)
Diabetes Mellitus	79 (39.5)	21 (10.5)	58 (29)
HIV	38 (19)	8 (4)	30 (15)
Other	93 (46.5)	38 (19)	55 (27.5)
CKD Stage *n*(%)			
3	52 (26)		
4	44 (22)		
5	104 (52)		

The study comprised 200 patients, all of whom had an eGFR putting them, at minimum, in stage 3 CKD. Females accounted for 60% (*n*=120) of the study participants, whilst 40% (*n*=80) were males.

Table 2: Descriptive statistics of eGFR

eGFR (ml/min/1.73m^2)		Male	Female
	Median	9.50	18
	IQR	±21	± 25.8
	Minimum	3	2
	Maximum	59	56

The ages of the entire cohort ranged from 18 to 84 years. The median age for the study group was 51 years, with a standard deviation of ±13.42. The median age of males versus females was different, with the females trending older than their male counterparts. The racial distribution of the study consisted of 55.5% (*n*=111) black patients of whom 43 were male and 68 were female, 41% (*n*=82) Indian patients of whom 33 were male and 49 were female, 2% (*n*=4) white patients of whom males and females were in equal number, 1% (*n*=2) coloured patients of whom males and females were also in equal number, and 1 (0.5%) male patient whose race was not documented.

Hypertension was the most frequently reported comorbidity in the study, with 80.5% (*n*=161) of patients suffering from this condition. There was a total of 46.5% (*n*=93) of patients with a comorbidity reported as ‘other’. This spectrum varied widely and included diagnoses such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA) and dyslipidaemia. Diabetes mellitus was the next most frequently reported comorbidity, with 39.5% (*n*=79) of patients having this diagnosis. Those who were HIV positive made up 19% (*n*=38) of the study population.

Table 3: Stages of CKD, broken down by race and gender

Stage	Total *n* (%)	Male	Female
3	52 (26) Black: 19 White: 0 Indian: 32 Coloured: 1 Unknown: 0	17	35
4	44 (22) Black: 25 White: 2 Indian: 16 Coloured: 0 Unknown: 1	13	31
5	104 (52) Black: 67 White: 2 Indian: 34 Coloured: 1 Unknown: 0	50	54

Those with stage 3 CKD comprised 26% (*n*=52) of the sample, those with stage 4 CKD comprised 22% (*n*=44) of the sample and those with ESRD predominated the sample at 52% (*n*=104).

Table 4 (on the next page): Descriptive statistics relating to medication use and dietetics assessment

Table 4	White			Indian			Coloured			Unknown	
	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male
ACEI	4	2	2	44	23	21	2	1	1	1	1
ARB	0	0	0	14	3	11	0	0	0	0	0
MRA	0	0	0	1	0	1	1	1	0	0	0
Loop diuretic	2	1	1	35	14	21	2	1	1	1	1
Sodium polystyrene sulphonate	0	0	0	5	1	4	0	0	0	0	0
Dietician (Seen)	3	2	1	53	25	28	2	1	1	1	1

Table 5: Number of patients per stage of CKD using ACEI, ARB and MRA

	Stage 3	Stage 4	Stage 5
ACEI	26	25	66
ARB	7	7	13
MRA	1	1	3

There were 58.5% (*n*=117) of the patients who were prescribed angiotensin-converting enzyme inhibitors (ACEI), and another 13.5% (*n*=27) who were prescribed angiotensin II receptor blockers (ARB). 52.5% (*n*=105) of the sample were prescribed the diuretic furosemide. Spironolactone, a mineralocorticoid antagonist (MRA), was prescribed to 2.5% (*n*=5) of the study sample. The prescribing differences regarding medication per stage of CKD is shown in Table 5. Of those patients with stage 3 CKD, 22.2% (*n*=26) of the total number of patients using ACEI (*n*=117) were prescribed ACEI, 25.9% (*n*=7) of the number using ARB (*n*=27) were prescribed ARB and 20% (n=1) of those using MRA (*n*=5) were prescribed this. Of those with stage 4 CKD on the RAAS blocking medication, 21.3% (*n*=25) were using ACEI, 25.9% (*n*=7) were using ARB and 20% (*n*=1) were using MRA. Amongst those with stage 5 CKD, 56.4% (n=66) were prescribed ACEI, 48.1% (n=13) were prescribed ARB and 60% (n=3) were known to be on MRA. The majority, 91% (*n*=182), was not prescribed the potassium lowering agent SPS. Only 4.5% (*n*=9) of the sample had been prescribed this potassium lowering agent, whilst its use in another 4.5% (*n*=9) was unknown. There was a dietician assessment for 72% (*n*=144) of patients, whilst 26.5% (*n*=53) had not yet been seen by a dietician.

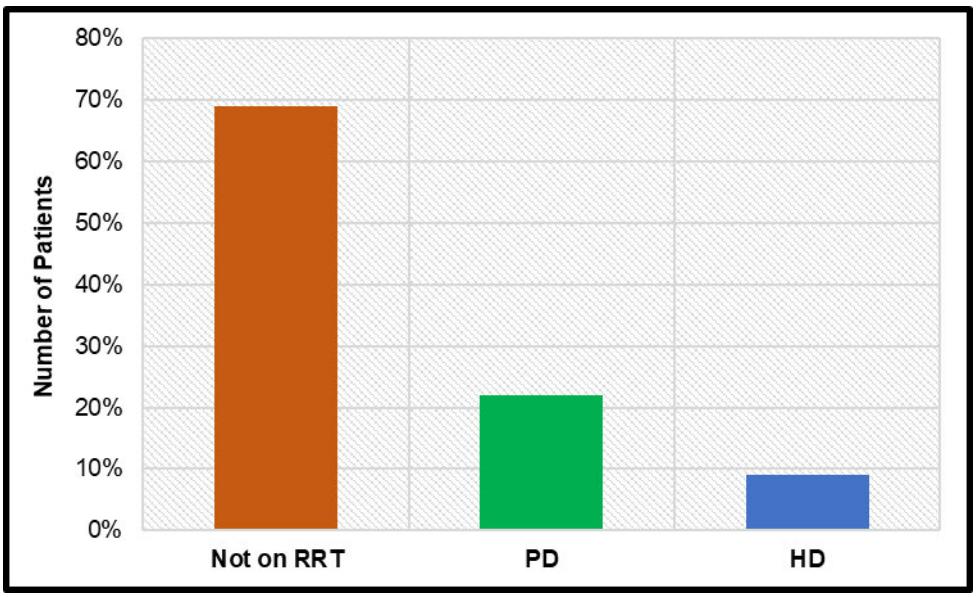

Figure 6: A bar graph depicting the percentage of patients on different forms of KRT (from left to right: none/PD/HD)

The largest proportion of the study sample, 69% (*n*=138) was found not to be on any form of KRT and were undergoing pharmacological management only. 22% (*n*=44) were undergoing PD and 9% (*n*=18) were undergoing HD.

Table 6: Mean potassium values by gender

Potassium (mmol/L)	Mean	Std error	Minimum	Maximum
	4.6	±0.05	2.50	6.60
Males	4.70	±0.09	2.50	6.50
Females	4.66	±0.07	2.50	6.60

The mean potassium was noted as being 4.6mmol/l, with a standard error of ±0.05. The highest single potassium value noted in any patient was 6.6mmol/l. The lowest single potassium value noted in any patient was 2.5mmol/l. There were 32 patients with a potassium level greater than or equal to 5.5mmol/l. The prevalence of hyperkalaemia in this study was thus 16%. Normokalaemia dominated the study; 78.5% (*n*=157) had potassium values that were within normal limits as defined in this study. Hyperkalaemia was present in 16% (*n*=32), of which 11% (*n*=22) was classified as mild, 4% (*n*=9) classified as moderate and 0.5% (*n*=1) classified as severe.

Of the patients with stage 3 CKD, the prevalence of hyperkalaemia was 7.69% (*n*=5).

Of the patients with stage 4 CKD, the prevalence of hyperkalaemia was 20.5% (*n*=9).

Of the patients with stage 5 CKD, the prevalence of hyperkalaemia was 17.3% (*n*=18).

Table 7: Levels of Potassium (low/normal/high)

Potassium Level (degree of hyperkalaemia)	*n*(%)
< 3.5mmol/L (hypokalaemia)	12 (6)
3.5 – 5.4mmol/L	157 (78.5)
5.5 – 5.9mmol/L (mild)	22 (11)
6.0 – 6.4mmol/L (moderate)	9 (4)
>6.5mmol/L (severe)	1 (0.5)

Table 8: Prevalence of Hyperkalaemia in Population with CKD

Stage of CKD	Overall hyperkalaemia $K^+ \geq 5.5$mmol/L *n* (%)	Mild hyperkalaemia K^+ 5.5 – 5.9mmol/L *n* (%)	Moderate hyperkalaemia K^+ 6.0 – 6.5mmol/L *n* (%)	Severe hyperkalaemia K^+ >6.5mmol/L *n* (%)
3	12 (7.69)	8(4)	3 (1.5)	1(0.5)
4	10(20.5)	8 (4)	2 (1)	0

5	10(17.3)	6 (3)	4 (2)	0
Form of KRT				
PD	7(15.9)	5(11.4)	2(4.54)	0
HD	2(11.1)	0	2(4.54)	0

Table 9: Variables assessed for association with hyperkalaemia

Variable	Odd's Ratio	95% Confidence Interval (CI) – lower	95% CI – upper	*p* value
Race	.068	-.054	.154	.337
Sex	-.021	-.255	.189	.770
Age	.091	-.003	.013	.200
CKD stage	-.027	-.153	.104	.709
HT	.037	-.201	.347	.601
DM	-.030	-.269	.175	.677
HIV	.011	-.254	.299	.873
ACEI	.014	-.176	.214	.848
ARB	-.014	-.233	.190	.840
MRA	.001	-.247	.249	.993
SPS	.144	.009	.482	.042
Dietician	.032	-.179	.286	.651

ARB = Angiotensin receptor blocker MRA = Mineralocorticoid receptor antagonist SPS = Sodium polystyrene sulfonate

Chapter 5: Discussion of Results

Access to quality healthcare for all patients has long been a problem in SA. Prior to the establishment of the first democratically elected government in 1994, specific health facilities were reserved for specific race groups. Although all healthcare services were technically available to patients across all race groups, this was made difficult by fewer hospitals catering to larger parts of the population. There has always been a paucity of healthcare services in more rural parts of SA. A study by Mhlanga et al., in 2020 found that racial differences still play a critical role in determining access to available public health sector services today. (23) Majority of the population relies on the public health sector, and the demand for these services has an influence on the overall quality of healthcare provided. This is not to say that quality of care is poor in the public sector, but that it is affected by longer waiting times at clinics, hospitals and pharmacies, a paucity of specialists across all fields, older infrastructure and often centralized tertiary and quaternary care, making this level of care difficult to access. (23,24)

A smaller section of the population has access to private health care services, usually by means of private medical insurance schemes. The same study by Mhlanga et al., calculated that 72% of whites and over 50% of South African Indians made use of private medical schemes, according to data reviewed from the General Household Survey (GHS) of 2016. Only 9.9% of black Africans had utilized private insurance, the rest relied on the public health sector to provide services. (23,24) 55.5% (n=111) of this study comprised of black patients, whilst Indians comprised of 41% (n=82) of the study group. There were very few white and coloured patients in the study sample (n=6). This is not in keeping with the racial demographics of the mid-year population estimates for South Africa from 2019. 7.9% of the total population was estimated to be white, whilst 8.8% of the total population were estimated to be coloured in that report from Statistics SA, with Indians only reported to comprise 2.6% of the total population. (25) However, outside of India, Durban does have the highest number of people of Indian descent living in the city, comprising about one quarter of the population and outnumbering the whites and coloureds living in this city. (26)

The 2019 population estimate put 51% of the total population of the country as being female. (25) Females predominated our study, with 60% of the participants documented as females. Males and females have biological differences which can result in different health needs and risks. These biological differences also result in differing needs from a healthcare system, resulting in more frequent usage from one gender. (25,26) Various studies have previously shown increased utilization of healthcare services by females. (26,27,28) Younger females access healthcare services more than males of a similar age, and this may be attributed to, in part, needs relating to contraception, pregnancy and postpartum complications. Although on the decline in recent years,

South Africa's maternal mortality and morbidity remains high. (25) Pregnancy related complications may also contribute to both acute and CKD in females.

The median age in our study population was found to be 51 years, with a standard deviation of ±13.42. In the United States of America (USA), 38% of those with CKD are aged 65 years or older. However, the life expectancy in the USA in 2020 was 77.0 years. (29) Life expectancy at birth in SA is 61.5 years for males and 67.7 years for females. (25) This median age is in keeping with CKD becoming more prevalent with age.

Majority of the study sample, 52% (*n*=104) had an eGFR which placed them in stage 5 CKD. By virtue of IALCH being the central referral hospital for nephrology in the province, we did expect to find more patients with ESRD. Most patients referred to the department are done so with the expectation that they will be considered for the transplant program and placed on interim KRT. Due to resource limitations in the public sector, the patients accepted for the program are those considered transplantable. These tend to be younger patients, with fewer comorbidities. (30,31) General Internal Medicine admissions in regional and district hospitals throughout the province are unlikely to see such levels of ESRD amongst their patient population.

Most patients, 69% (*n*=138), were being managed by pharmacological therapy alone and had not been initiated on any form of RRT. There was 31% (*n*=62) of the sample was on KRT, with 22% of the total study sample (*n*=44) on PD and 9% of the total study sample (*n*=18) on HD. The public health sector in KZN uses a "PD first" approach. Patients who present with renal failure requiring dialysis are initiated on PD, usually via the insertion of a temporary indwelling PD catheter. There are some exceptions to this, those patients in whom PD catheter insertion is contraindicated such as due to severe, active inflammatory bowel disease, active abdominal sepsis or prior extensive abdominal surgery (relative contraindication). (32,33) Patients admitted in an ICU setting are more likely to be initiated on haemodialysis should they require KRT. South Africa accounts for around 85% of all PD KRT cases in Africa. (32,33) Most patients requiring chronic KRT in our setting undergo continuous ambulatory peritoneal dialysis (CAPD), via a permanent indwelling catheter. (33) The majority of these are inserted intraoperatively at IALCH, but there are centers such as King Edward VIII Hospital where the temporary dialysis catheters are converted to tunneled permanent catheters at the bedside, using an aseptic technique. HD centers and slots are limited, and access to centers is limited to those living in outlying areas. (33) Both forms of KRT are not without their complications. The most common complication on those undergoing CAPD is peritonitis. Depending on the offending organism and the severity of peritonitis, this may require removal of the permanent indwelling catheter and conversion of these patients to HD. (33,34) As previously documented in this report, there remains a paucity of nephrologists and public dialysis centers in KZN. (2) CAPD can be performed as an outpatient,

with the patient performing several exchanges per day themselves. Additional challenges to CAPD for patients living in outlying areas or poor social circumstances include the lack of access to clean water and water restrictions in some areas. (32,33,34)

The most prevalent comorbidity in this study was hypertension (HT), with 80.5% (*n*=161) of patients known with this condition. As renal function deteriorates, BP does become increasingly difficult to control. (35) This is in addition to the possibility that hypertensive nephrosclerosis was contributory to the progression to CKD in these patients. (35,36) There were 39.5% (*n*=79) of the study sample who were documented to have diabetes mellitus (DM). Diabetic nephropathy is an important contributor to the spectrum of patients with CKD. (37) Thus, the importance of measuring the U-ACR at diabetic follow up clinics, to identify patients who may have developed microalbuminaemia. Early initiation of treatment is useful to delay disease progression. (37) Drugs used to limit albumin loss in urine are also within the category of antihypertensives. Control of BP is incredibly important to delay progression of CKD once renal physiological and structural changes are present in patients with DM. (35,36,37) The estimated overall prevalence rate of HIV is 13.7% in the South African population. In our study, it was 19% (*n*=38). (25) Typically, patients with unsuppressed HIV viral loads (VL) who are not on antiretroviral therapy (ART) are not considered suitable candidates for the state renal program. Patients with suppressed VL who have been on ART for at least 6 months are suitable candidates. (31,32) HIV positive patients are at risk for a variety of renal complications, this includes those patients with suppressed VL on ART. Patients are susceptible to drug related renal toxicity, acute kidney injury relating to a variety of precipitants and HIV associated nephropathy (HIVAN). (38) Nearly half, 46.5% (*n*=93), of patients in the study were diagnosed with a condition other than HT, DM and HIV. This spectrum was wide, and included diagnoses such as SLE, RA and cardiac failure amongst others. The autoimmune conditions, such as SLE and RA, have well documented renal manifestations, relating to both the conditions themselves as well as drug related toxicity. (39,40)

Despite ACEI and ARB both being known to result in hyperkalaemia, this study did not find any significant correlation between these drugs and potassium level. (41) A significant portion of the study sample 58.5% (*n*=117) was using ACEI. More than half of the study sample 52.5% (*n*=105) were prescribed the loop diuretic furosemide. Extracellular fluid volume increases in CKD, and loop diuretics are recommended in the management of this. Loop diuretics are more effective than other diuretics when eGFR is <30ml/min/1.73m^2, however the diuretic response to furosemide is also decreased in CKD. (42) There was no significant correlation found between use of the loop diuretic furosemide and potassium levels. Patients who had been prescribed SPS were 4.5% of the sample (n=9). There was a significant correlation between use of SPS and potassium levels, with *p* value <0.05. As patients with hyperkalaemia are treated with SPS, this was not surprising.

ACEI and ARB, as well as MRA, are important medications in patients with CVD. As mentioned, CKD is an independent risk factor CVD. Although our study did not show hyperkalaemia being more prevalent in patients on these agents, it is known that their use may result in hyperkalaemia. One of the mainstays for slowing progression of CKD remains optimal control of blood pressure. Agents acting on the Renin Angiotensin Aldosterone System (RAAS), such as ACEI and ARB, are well studied and provide both renal and cardiac protection in CKD. ACEI and ARB are the preferred agents in diabetic patients with proteinuria, even without the presence of hypertension. RAAS agents delay progression of CKD. (43) Hyperfiltration in the kidneys causes sclerosis, which begins a vicious cycle of hyperfiltration and ongoing sclerosis. ACEI lead to decreased hyperfiltration by decreasing glomerular capillary pressure, therefore causing dilatation of the efferent arteriole. This is likely mediated by AT II inhibition, as well as bradykinin augmentation. As ARB don't have activity to increase bradykinin, they don't decrease glomerular pressures to the same extent as ACEI. However, both types of agents show efficacy in slowing the progression of CKD. (44)

The Eighth National Joint Committee (JNC 8) do not recommend dual RAAS blockade using both ACEI and ARB as this has been shown to increase the odds of hyperkalaemia in these patients. Previous studies in CKD show treatment with RAAS blocking agents to be associated with higher risk of hyperkalaemia. A meta-analysis by Zhang et al in 2020 did show that patients on ACEI or ARB monotherapy had higher odds of hyperkalaemia. A study by Hsu et al in JAMA Internal Medicine showed higher hyperkalaemia associated hospitalisations in patients on ACEI or ARB, but those with hyperkalaemia did not have significantly increased risk of death. (43,44,48)

Often these drugs are discontinued when a patient develops hyperkalaemia. Keeping potassium within a specified range is essential for proper metabolic function, however there are also several studies which have shown the benefits in the use of ACEI/MRA/ARB in patients with pre-existing cardiac disease. (45,46) Mortality benefit has been noted with the use of these agents in patients known with congestive cardiac failure. In cases where hyperkalaemia is also present, it may be detrimental to withhold the use of these agents. SPS is the most used potassium binder in our setting, for in and outpatients. However, the onset and peak of action of this drug leaves something to be desired. It is also not without side effects, in particular gastrointestinal effects, and patients are also at risk of hypokalaemia after its administration, especially with the use of multiple doses. (47,48) 2 newer agents for the management of hyperkalaemia have received FDA approval: Patiromer Sorbitex Calcium and Sodium Zirconium Cyclosilicate. Patiromer has been shown to decrease serum potassium in cases of acute, non-life-threatening hyperkalaemia within 6 hours of administration, as well as to decrease the recurrence of hyperkalaemia. It is usually given as a once off oral administration. This is easier for patients and nursing staff to administer, opposed to the

more frequent dosing of SPS. As it is known that the abovementioned agents (ACEI/ARB/MRA) may have nephroprotective effects in patients with pre-existing CVD and CKD, and the use of agents such as Patiromer to manage hyperkalaemia may allow patients to continue the maximum beneficial dose for themselves without the worry of ongoing hyperkalaemia. (45,48,50)

Referral to a dietician is important for patients with CKD, especially those with ESRD. Patients diagnosed with HT are often prescribed the Dietary Approaches to Stop Hypertension (DASH) diet. This dietary advice is based on 2 studies, DASH and DASH-Sodium, that looked at ways of improving BP control with changes in diet. The DASH diet is high in fruits, vegetables and low-fat dairy products, whilst being lower in fat and cholesterol. BP was lowered within 2 weeks of starting the diet, and cholesterol levels were found to be reduced as well. DASH-Sodium prescribed 3 eating plans with differing levels of sodium concentration. BP was lowered for everyone on the diet, but those with the most restricted sodium concentrations had greater drops in BP. (45,46) Although these approaches may seem logical, it is still important to discuss them with patients and ensure that they are advised accordingly. Fluid and protein restriction are also important parameters to discuss, especially in those patients on KRT who are anuric. A clearly documented eating plan is helpful to patients to serve as a reminder of what their diets should entail in order to optimize both their comorbidities as well as the progression of CKD. The majority, 72% (n=144), were documented to have been seen by the dietician. Despite this not reaching statistical significance versus those who had not seen a dietician and those whose status was unknown; it remains imperative that patients are educated on the correct diet in order to prevent increased dietary intake of potassium as well as to ensure that they do not develop fluid overload.

Using the previously mentioned definition of hyperkalaemia, 78.5% (n=157) of the study sample had a potassium that was within the normal range. The overall prevalence of hyperkalaemia was found to be 16%. This is lower than the prevalence described in a study from a renal department in Greece, which was 22.7%, however that study used the lower cutoff point of potassium greater than 5mmol/L being defined as hyperkalaemia. In the work by Humphrey et al, previously mentioned in Chapter 2, the prevalence of hyperkalaemia by any definition was found to be 6.3% across all adult studies. Hyperkalaemia was highest amongst those with known kidney injury, with 21.5% of patients with ESRD having had an episode of hyperkalaemia. A 2017 study by Nilsson et al found that the incidence proportion of hyperkalaemia was higher amongst patients with more frequent potassium measurements (1.6%, 8.4% and 32.3% among those assessed 1-22, 2-4 and >4 times per year. In this study, only 1 potassium value was used per patient. This may have had some influence on the prevalence we obtained. The incidence proportion was also higher among

suspected comorbid populations, including those with CKD. This is in keeping with our study, in which the majority of the study population had ESRD.(53) Hypokalaemia -as present in 6% (*n*=12) of the study sample, with potassium levels lower than 3.5mmol/L.

There were no associations found between the presence of hyperkalaemia and the mode of KRT, the comorbidities of the patient or a previous dietician consult. There were 20.5% (*n*=9) of the patients with hyperkalaemia that had stage 4 CKD, whilst 17.3% (*n*=18) had stage 5 CKD. There were 52% (*n*=104) patients with stage 5 CKD, and of these 59.6% (*n*=62) were not on a form of KRT, 70.9% (*n*=44) on PD and 29% (*n*=18) on HD. The majority, 69% (*n*=138), of patients were not on KRT and were being managed by pharmacological treatment alone.

Chapter 6: Study Limitations

As this is a retrospective study, limitations are to be expected. The study was undertaken at IALCH, which is the central hospital for quaternary care in KZN. By virtue of this, we expected to see a larger number of patients with ESRD. It was also expected to find patients with more comorbidities, despite the degree of renal dysfunction at referral. Thus, the study may have been affected by sampling bias as those with worse renal function and more comorbidities predominated the sample. The study included only patients 18 years and older; however, those as young as 12 years old are referred to treatment centers as adults in KZN.

Prior to referral to IALCH, all patients must have a renal proforma completed and sent through to the Department of Nephrology. Once received, they are collated, and patients are assigned appointment dates based on degree of renal dysfunction. Those patients who are currently receiving any form of dialysis at an outside center are ideally accepted for admission and seen as inpatients. This proforma includes various details about patient demographics, anthropometry, comorbidities and current medication. Those patients whose initial visit is as an inpatient admission usually come with detailed referral letters and results of investigations. However, those who are seen at the clinic do not always arrive with referral letters or proformas, making it difficult to capture some of data that would have been reflected on a proforma/referral letter. Often patients are unaware of their exact diagnoses and medication. Thus, all details may not have captured for all patients.

Summary and Recommendations

The specific objectives set out at the start of the study have been achieved. We have determined the prevalence of hyperkalaemia, and prevalence of hyperkalaemia per CKD stage. The overall prevalence of hyperkalaemia at the renal clinic at IALCH was 16%. Of those with hyperkalaemia, the majority had mild elevation of potassium. Only one patient had severe hyperkalaemia. The prevalence of hyperkalaemia in those with stage 3 CKD was 7.69%, in those with stage 4 CKD it was 20.5% and in those patients with stage 5 CKD the prevalence of hyperkalaemia was 17.3%.

This study did not find associations between demographic factors such as age, gender and race with the presence of hyperkalaemia. This study did not find associations between the presence of HT, DM and HIV with the presence of hyperkalaemia. There were no associations found between the use of ACEI, ARB, MRA and loop diuretics and the presence of hyperkalaemia. The presence of hyperkalaemia was not shown in this study to be influenced by the mode of KRT. There was a statistically significant association with the use of SPS. The abovementioned findings were also part of the study objectives.

Although there was no statistically significant difference in the potassium levels of those who had seen the dietician versus those who had not, it is still recommended for all patients with CKD to be seen by a dietician. Patients with HT and DM should also have intensive dietary counselling in order to delay the onset and progression of CKD. Patients with ESRD on KRT should also have intensive dietary counselling, especially those who are anuric.

The racial breakdown of the study was different from the population statistics of the country, in that there was a large representation of Indian patients in the study sample whilst their presence in the general population is low. As previously mentioned, the representation of Indian patients in Durban is much higher than the national average. Previous studies have shown that South African Indians have a high prevalence of T2DM, and one of the known microvascular complications is that of diabetic nephropathy. (45) It would be interesting to study this group of patients further to identify and understand the risk factors associated with the development of CKD in Indians.

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Appendix 1: Final Protocol

Title of the Study:

A retrospective study to determine the prevalence and degree of hyperkalaemia in adult patients with chronic kidney disease, attending the renal clinic at Inkosi Albert Luthuli Central Hospital.

Aim of Study:

To determine the prevalence and degree of hyperkalaemia in adult patients with chronic kidney disease, attending the renal clinic at Inkosi Albert Luthuli Central Hospital, and to determine the role, if any, that variable demographic parameters and comorbidities may have on this prevalence.

Specific objectives:

1. To determine the prevalence of hyperkalaemia in patients with chronic kidney disease attending the renal clinic at Inkosi Albert Luthuli Central Hospital.
2. To determine the degree of hyperkalaemia of each patient according to the stage of chronic kidney disease.
3. To determine the difference in prevalence of hyperkalaemia between those with chronic kidney disease not on renal replacement therapy, and those undergoing peritoneal dialysis and/or haemodialysis.
4. To assess the association of variables such as age, gender, ethnicity, stage of chronic kidney disease and comorbidities that may have an impact on the prevalence of hyperkalaemia within this group of patients.

Study Design:

Study Population:

The study population will comprise 200 patients with chronic kidney disease including those not yet receiving renal replacement therapy as well as patients with end stage renal disease undergoing peritoneal dialysis and patients with end stage renal disease undergoing haemodialysis at IALCH, who are attending the renal clinic at IALCH and were assessed both clinically and biochemically within the study period.

Sampling strategy and statistical planning and analysis:

This is a retrospective, descriptive study.

A minimum of 200 patients seen consecutively during the study period will be selected.

Inclusion Criteria:

This study includes patients 18 years and older, attending the renal clinic at Inkosi Albert Luthuli Central Hospital with a diagnosis of chronic kidney disease, between 1 October 2016 and 30 September 2017.

Exclusion Criteria:

This study excludes patients younger than 18 years of age.

Data collection methods and Tools:

1. The data collection period will fall between 1 October 2016 and 30 September 2017.
2. A list of patients will be generated from a computerised data mining system. Once this has occurred, consecutive files will be selected and reviewed until a minimum number of 200 is reached.
3. Information relating to the patients' age, gender, ethnicity and comorbidities will be collected from the information recorded as computerised data on the hospital system at IALCH.
4. Blood results relating to each visit will be collected from the information recorded as computerised data on the hospital system at IALCH.
5. The data will be captured and subsequently analysed using the SPSS (Statistical Packages for Social Sciences V25) and the statistical tools used will be descriptive, cross tab, correlation and regression statistics.

Study Location:

Inkosi Albert Luthuli Central Hospital

Durban, South Africa

Study Period:

1 October 2016 to 30 September 2017.

Limitations to the study:

1. This study only includes patients with chronic kidney disease attending the renal clinic at Inkosi Albert Luthuli Central Hospital, which is a quaternary level public sector hospital. Consequently, the proportion of patients with advanced stages of chronic kidney disease is expected to be higher.
2. This study only includes patients 18 years or older.
3. This study is retrospective.

Ethical considerations:

This is a descriptive, retrospective study. However, all patient data will be deidentified and patient confidentiality maintained. Ethical approval will be sought from BREC.

Appendix 2: Protocol Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

12 December 2017

Prof AGH Assounga
Department of Nephrology

Dear Prof Assounga

MMED PROTOCOL: "A retrospective study to determine the prevalence and degree of hyperkalaemia in adult patients with chronic kidney disease, attending the renal clinic at Inkosi Albert Luthuli Central Hospital"
Student: Dr T Bux, Student Number: 217080529 (Department of Medicine)

I am pleased to inform you that the abovementioned protocol has been approved.

Please note:

- The Academic Leader: School Research must review any changes made to this study.
- The study may not begin without the approval of the Biomedical Research Ethics Committee.
- A copy of the full ethics approval letter should be forwarded to the Postgraduate Office.

May I take this opportunity to wish the student every success with the study.

Yours sincerely

Lushy Konar
Postgraduate Administrator

CC Dr T Bux

Biomedical Research Ethics Committee
Westville Campus

Postgraduate, Higher Degrees & Research
School of Clinical Medicine, NRMSM Campus
Postal Address: P/Bag X3, Congella, Durban, 4013, South Africa
Telephone: +27 (0) 31 260 4416 **Facsimilie:** +27 (0) 31 260 4723 **Email:** konar@ukzn.ac.za **Website:** www.ukzn.ac.za

Appendix 3: BREC Approval

UNIVERSITY OF KWAZULU-NATAL
INYUVESI YAKWAZULU-NATALI

14 August 2018

Dr T Bux (217080529)
School of Clinical Medicine
College of Health Sciences
Tas.bux@gmail.com

Protocol: A retrospective study to determine the prevalence and degree of hyperkalaemia in adult patients with chronic kidney disease, attending the renal clinic at Inkosi Albert Luthuli Central Hospital.
Degree: MMed

BREC Ref No: BE019/18

EXPEDITED APPLICATION: APPROVAL LETTER

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 19 December 2017.

The study was provisionally approved pending appropriate responses to queries raised. Your response received on 27 August 2018 to BREC letter dated 18 July 2018 have been noted by a sub-committee of the Biomedical Research Ethics Committee. The conditions have now been met and the study is given **full ethics approval** and may begin as from **14 September 2018**. Please ensure that site permissions are obtained and forwarded to BREC for approval before commencing research at a site.

This approval is valid for one year from **14 September 2018.** To ensure uninterrupted approval of this study beyond the approval expiry date, an application for recertification must be submitted to BREC on the appropriate BREC form 2-3 months before the expiry date.

Any amendments to this study, unless urgently required to ensure safety of participants, must be approved by BREC prior to implementation.

Your acceptance of this approval denotes your compliance with South African National Research Ethics Guidelines (2015), South African National Good Clinical Practice Guidelines (2006) (if applicable) and with UKZN BREC ethics requirements as contained in the UKZN BREC Terms of Reference and Standard Operating Procedures, all available at http://research.ukzn.ac.za/Research-Ethics/Biomedical-Research-Ethics.aspx.

BREC is registered with the South African National Health Research Ethics Council (REC-290408-009). BREC has US Office for Human Research Protections (OHRP) Federal-wide Assurance (FWA 678).

The sub-committee's decision will be noted by a full Committee at its next meeting taking place on **09 October 2018.**

We wish you well with this study. We would appreciate receiving copies of all publications arising out of this study.

Yours sincerely

[redacted]

Prof V Rambiritch
Chair: Biomedical Research Ethics Committee

cc postgraduate administrator: konar@ukzn.ac.za
cc supervisor: assoungaa@ukzn.ac.za

Appendix 4: Hospital/Gatekeeper Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

Office of The Medical Manager
IALCH

Reference: BE019/17
Enquiries: Medical Management

16 April 2018

Dr T Bux
School of Clinical Medicine
College of Health Sciences

Dear Dr Bux

RE: PERMISSION TO CONDUCT RESEARCH AT IALCH

I have pleasure in informing you that permission has been granted to you by the Medical Manager to conduct research on: **A retrospective study to determine the prevalence and degree of hyperkalaemia in adult patients with chronic kidney disease, attending the renal clinic at Inkosi Albert Luthuli Central Hospital.**

Kindly take note of the following information before you continue:

1. Please ensure that you adhere to all the policies, procedures, protocols and guidelines of the Department of Health with regards to this research.
2. This research will only commence once this office has received confirmation from the Provincial Health Research Committee in the KZN Department of Health.
3. Kindly ensure that this office is informed before you commence your research.
4. The hospital will not provide any resources for this research.
5. You will be expected to provide feedback once your research is complete to the Medical Manager.

Yours faithfully

[redacted] Dr Nevisha Tahlali

Dr L P Mtshali pp/Acting
Medical Manager

Appendix 4: Hospital/Gatekeeper Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

DIRECTORATE:

Physical Address: 800 Bellair Road, Mayville, 4058
Postal Address: Private Bag X08, Mayville, 4058
Tel: 0312401059 Fax: 0312401050 Email: ursulanun@ ialch.co.za
www.kznhealth.gov.za

Office of The Medical Manager
IALCH

16 April 2018

Dr T Bux
School of Clinical Medicine
College of Health Sciences

Dear Dr Bux

Re: Approved Research: Ref No: BE019/18: A retrospective study to determine the prevalence and degree of hyperkalaemia in adult patients with chronic kidney disease, attending the renal clinic at Inkosi Albert Luthuli Central Hospital.

As per the policy of the Provincial Health Research Committee (PHRC), you are hereby granted permission to conduct the above mentioned research once all relevant documentation has been submitted to PHRC inclusive of Full Ethical Approval.

Kindly note the following.

1. The research should adhere to all policies, procedures, protocols and guidelines of the KwaZulu-Natal Department of Health.
2. Research will only commence once the PHRC has granted approval to the researcher.
3. The researcher must ensure that the Medical Manager is informed before the commencement of the research by means of the approval letter by the chairperson of the PHRC.
4. The Medical Manager expects to be provided feedback on the findings of the research.
5. Kindly submit your research to:

   The Secretariat
   Health Research & Knowledge Management
   330 Langaliballe Street, Pietermaritzburg, 3200
   Private Bag X9501, Pietermaritzburg, 3201
   Tel: 033395-3123, Fax 033394-3782
   Email: hrkm@kznhealth.gov.za

Yours faithfully

Mtshali /Dr Nonsha Tatwah

Dr L P Mtshali pp/Actng
Medical Manager

Appendix 4: Hospital/Gatekeeper Approval

PO Box 72988
Mobeni
4060

27 March 2018

To: Hospital Manager, Inkosi Albert Luthuli Central Hospital

Re: PROTOCOL

Permission is requested to conduct the above research study at the hospital indicated below:

Site 1 address:

Inkosi Albert Luthuli Central Hospital

Investigator/s:

Principal: [redacted]

Co-investigator:

Co-Investigator:

Signatu[redacted]er :

Date: 17/04/2018

Dr Nevisha Tathwah

Site 2 address: Investigator/s

Principal:

Co-investigator:

Co-Investigator:

Signature of Hospital Manager :

Date:

Please find attached copies of the accepted research protocol, as well as the acceptance letter from the UKZN postgraduate committee and the provisional BREC approval.

NB: Hospital Manager/s to send a copy of this document to Natalia.

Kind regards

[redacted]

Dr T. Bux
MBChB (Pret.)
Registrar: Internal Medicine
Contact: 079 898 5017
Email: tas.bux@gmail.com

Appendix 5: Department of Health Approval

health
Department:
Health
PROVINCE OF KWAZULU-NATAL

Physical Address: 330 Langalibalele Street, Pietermaritburg
Postal Address: Private Bag X9051
Tel: 033 395 2805/ 3189/ 3123 Fax: 033 394 3782
Email:
www.kznhealth.gov.za

DIRECTORATE:
Health Research & Knowledge Management

HRKM Ref: 293/18
NHRD Ref: KZ_201807_035

Dear Ms T. Bux
UKZN

Approval of research

1. The research proposal titled **'A retrospective study to determine the prevalence and degree of hyperkalaemia in adult patients with chronic kidney disease, attending the renal clinic at IALCH'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Inkosi Albert Luthuli Central Hospital.

2. You are requested to take note of the following:
   a. Make the necessary arrangement with the identified facility before commencing with your research project.
   b. Provide an interim progress report and final report (electronic and hard copies) when your research is complete.

3. Your final report must be posted to **HEALTH RESEARCH AND KNOWLEDGE MANAGEMENT, 10-102, PRIVATE BAG X9051, PIETERMARITZBURG, 3200** and e-mail an electronic copy to hrkm@kznhealth.gov.za

For any additional information please contact Mr X. Xaba on 033-395 2805.

Yours Sincerely

[redacted]

Dr E Lutge

Chairperson, Health Research Committee

Date: 14/08/18