EPIDEMIOLOGY OF CHRONIC KIDNEY DISEASE IN KWAZULU-NATAL: EVALUATION OF RISK FACTORS, COMPLICATIONS AND DIAGNOSTIC METHODS

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MBChB, MMed (Natal); MSc Epidemiology (London); FCP (SA)

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Submitted in fulfilment of the requirements for the degree of
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DECLARATION

I, **Nomandla Daphne Madala**, declare as follows:

1. That the work described in this thesis has not been submitted to UKZN or other tertiary institution for purposes of obtaining an academic qualification, whether by myself or any other party.

2. That my contribution to the project was as follows:
   2.1. I conceived the study, developed the draft protocols, reconciled revisions from supervisors and co-authors, submitted final protocols for ethical approval.
   2.2. I undertook patient consultations at both study sites, collected, analysed and interpreted the data.
   2.3. I wrote the draft manuscripts, reconciled input from co-authors and submitted the final manuscripts.

3. That the contributions of others to the project were as follows:
   3.1. Professors A.G.H. Assounga and S. Naicker were my PhD supervisor and co-supervisor, respectively, who supervised the research. They provided intellectual input into the research study protocols and in revision of the draft as well as the final manuscripts.

   3.2. Professor A.G.H. Assounga provided training to the late Dr G.P. Thusi that facilitated the establishment of the outreach CKD clinic study site at Ngwelezana Hospital, Empangeni, northern KwaZulu-Natal (Chapter 2).

   3.3. Dr G.P. Thusi was responsible for establishing the outreach CKD clinic, participated in data collection and in the initial draft manuscript (Chapter 2).

   3.4. Professor N.P. Magula provided intellectual input in the protocol development as well as assisted in data collection and writing the manuscript (Chapter 5).

   3.5. Mrs N. Nkwanyana assisted with performing some of the statistical analysis (Chapters 5 and 6).

   3.6. Dr T. Dubula participated in data collection and provided input in the initial draft as well as final submitted manuscript (Chapter 3 and 6).

   3.7. Miss O.M. Oluyede and Prof J.R. Tapamo performed the mathematical modelling, data analysis and developed the new eGFR equation in Africans (Chapter 7).

Signed: [redacted] Date: _____

Supervisors: Prof AGH Assounga _____ Date: _____

Prof S Naicker _____

DEDICATION

To my dear parents

Mrs Patricia Alice Ndileka ‘Nondie’ Madala
MaNkala, just as you committed during my early school years,
Your shoulders indeed became the springboard for me to launch into space.

and

late Judge Tholakele ‘Tholie’ Hope Madala
Pop, you were taken from us much too soon and are dearly missed.
Your unfailing confidence in me under all circumstances continues to inspire me daily.
Rest in eternal peace, Tshabalala, Mtshengu, Sobhuza!

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LIST OF ACRONYMS

Abbreviation	Description
^{99m}Tc-DTPA	Technicium-99m-diethylenetriaminepentaacetic acid
ACE	Angiotensin converting enzyme
ADPKD	Autosomal dominant polycystic kidney disease
ARB	Angiotensin-II receptor blocker
BMI	Body mass index
BSA	Body surface area
CAPD	Continuous ambulatory peritoneal dialysis
CG	Cockcroft-Gault
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRP	C-reactive protein
CVD	Cardiovascular disease
DEXA	Dual X-ray absorptiometry
eGFR	Estimated glomerular filtration rate
ESRD	End stage renal disease
GFR	Glomerular filtration rate
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HD	Haemodialysis
HIV	Human immunodeficiency virus
HIVAN	HIV-associated nephropathy
IDMS	Isotope dilution mass spectrometry
IHD	Ischaemic heart disease
KDIGO	Kidney Disease: Improving Global Outcomes
K-DOQI	Kidney Dialysis Outcomes Quality Initiative
LV	Left ventricle
MDRD	Modification of Diet in Renal Disease
mGFR	Measured glomerular filtration rate
NHLS	National Health Laboratory Services
P_{30}	Percentage of estimates within 30% of measured GFR
PEW	Protein energy wasting

RMSE	Root mean square error
RRT	Renal replacement therapy
SADTR	South African Dialysis and Transplant Registry
SARR	South African Renal Registry
WHO	World Health Organization
WHtR	Waist-to-height ratio

ABSTRACT

Background

Chronic kidney disease (CKD) is associated with increased morbidity and mortality as well as costly renal replacement therapy. The aim was to determine risk factors and complications that contribute to morbidity as well as a suitable diagnostic detection method for CKD.

Methods

Observational studies were done at 2 hospitals. To assess risk factors, 283 patients were included at the Durban site, and sub-studies undertaken within this sample for CKD complications, while 302 patients were studied at the Empangeni outreach site. To evaluate predictive performance of estimated glomerular filtration rate (eGFR), data from 148 patients were analysed. A further 76 patients were recruited, to develop an African equation. Cockcroft-Gault, Modified Diet in Renal Disease and CKD Epidemiology Collaboration eGFR equations were compared with technicium-99-mdiethylenetriaminepentaacetic acid (^{99m}Tc-DTPA)-GFR as the gold standard. Body composition was assessed by anthropometry and dual energy X-ray absorptiometry. Data were analysed with STATA.

Results

The commonest CKD risk factors were hypertension (75%), diabetes (29%) and human immunodeficiency virus (HIV) infection (24%), with HIV commoner at the outreach site (28.5% vs 19.8%). Over 80% of females and ~60% males were overweight/obese overall; however, clinical cardiovascular disease was commoner in Durban (28% vs 5%). Complications were observed in early CKD; prevalence increased as eGFR declined from ≥90 ml/min/1.73m^2 to <30 ml/min/1.73m^2: hyperuricaemia increased from 17% to 74%, metabolic acidosis (11.6% to 72.7%), anaemia (2.9% to 69.7%), hyperphosphataemia (10.1% to 48.5%), all p<0.001, respectively, and hypocalcaemia from 1.5% to 18.2% (p=0.003). Lower GFR levels were also associated with lower serum albumin levels, and lower whole body as well as regional lean mass and fat mass in males. A further observation at GFR <30 ml/min/1.73m^2 was that eGFR underestimated ^{99m}Tc-DTPA-GFR in African patients. Prediction of ^{99m}Tc-DTPA-GFR was also poor at GFR levels ≥60 ml/min/1.73m^2, with eGFR overestimating ^{99m}Tc-DTPA-GFR. An eGFR equation developed in African patients resulted in significantly better GFR prediction and showed the lowest bias, highest precision as well as accuracy.

Conclusion

Efforts are needed to enable non-nephrologists to manage CKD risk factors and complications. Prediction of GFR may be substantially improved by using an equation developed in Africans.

CHAPTER 1

INTRODUCTION

1.1. BACKGROUND AND CONTEXT OF THE RESEARCH WORK

The worldwide incidence of end stage renal disease (ESRD) grew exponentially over the last two decades due to the growing burden of diabetes mellitus, which has become the commonest cause of ESRD in developed countries. In contrast data from South Africa and sub-Saharan Africa have shown hypertension as the commonest cause in the region. However, these data are inaccurate due to the lack of renal registries in most sub-Saharan African countries. The diabetes burden in the region is increasing due to urbanization while HIV, another cause of ESRD, is at pandemic proportions. Epidemiological data on these emerging ESRD causes in South Africa are needed to inform health service planning because the availability of ESRD treatment is severely limited due to resource constraints. Chronic kidney disease (CKD) early detection programs aimed at retarding progression thus reducing incidence of ESRD are urgently needed. These require that CKD diagnosis can be made easily and cost-effectively in routine clinical practice but currently used methods developed elsewhere may be inaccurate in Africans.

1.1.1. DEFINITION AND CLASSIFICATION OF CHRONIC KIDNEY DISEASE

The 2002 Kidney Dialysis Outcomes Quality Initiative (K-DOQI) Clinical Practice Guidelines provided a clear definition for CKD that included classification according to level of glomerular filtration rate (GFR) (1). The K-DOQI guidelines have since been reviewed and replaced with the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guidelines to improve CKD outcomes (2). Staging of CKD now considers GFR (Table 1.2) as well as albuminuria (Table 1.3) while both markers are also used in risk stratification, to predict complications and future outcomes (Table 1.4).

Table 1.1. Definition of CKD (2)

Criteria for CKD (either of the following present for ≥3 months)	
Markers of kidney damage (one or more)	Albuminuria Albumin excretion rate ≥30 mg/24 hours; Albumin: creatinine ratio ≥30 mg/g (≥3 mg/mmol) Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased GFR	GFR <60 ml/min/1.73 m^2 (GFR categories G3a–G5)

CKD, chronic kidney disease; GFR, glomerular filtration rate. Reprinted from Kidney Int Suppl., vol 3, Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group (2). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, pages 1-150, 2013, with permission from Elsevier; accessed at http://dx.doi.org/10.1038/kisup.2012.64

Table 1.2. Staging of CKD by categories of glomerular filtration rate (2)

GFR categories in CKD		
GFR category	**GFR (ml/min/1.73m^2)**	**Terms**
G1	≥90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

CKD, chronic kidney disease; GFR, glomerular filtration rate. Reprinted from Kidney Int Suppl., vol 3, Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.(2) KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, pages 1-150, 2013, with permission from Elsevier; accessed at http://dx.doi.org/10.1038/kisup.2012.64

Table 1.3. Staging of CKD by categories of albuminuria (2)

Albuminuria categories in CKD				
Category	**Albumin excretion rate (mg/24 hours)**	**Albumin: creatinine ratio (approximate equivalent)**		**Terms**
		(mg/mmol)	**(mg/g)**	
A1	<30	<3	<30	Normal to mildly increased
A2	30-300	3-30	30-300	Moderately increased
A3	>300	>30	>300	Severely increased

CKD, chronic kidney disease. Reprinted from Kidney Int Suppl., vol 3, Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.(2) KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, pages 1-150, 2013, with permission from Elsevier; accessed at http://dx.doi.org/10.1038/kisup.2012.64

Table 1.4. Predicting prognosis of CKD (2)

GFR categories (ml/min/ 1.73 m2) Description and range	Prognosis of CKD by GFR and Albuminuria Categories			Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<3 mg/mmol <30 mg/g	3-30 mg/mmol 30-300 mg/g	>30 mg/mmol >300 mg/g
	G1	≥90	Normal or high			
	G2	60-89	Mildly decreased			
	G3a	45-59	Mildly to moderately decreased			
	G3b	30-44	Moderately to severely decreased			
	G4	15-29	Severely decreased			
	G5	<15	Kidney failure			

CKD, chronic kidney disease; GFR, glomerular filtration rate. Green: low risk (if no other markers of kidney disease, no CKD); Yellow: moderately increased risk; Orange: high risk; Red, very high risk. Reprinted from Kidney Int Suppl., vol 3, Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group.(2) KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease, pages 1-150, 2013, with permission from Elsevier; accessed at http://dx.doi.org/10.1038/kisup.2012.64

1.1.2. GLOBAL PUBLIC HEALTH IMPACT OF CHRONIC KIDNEY DISEASE

Efforts aimed at CKD prevention and early detection grew significantly over the past decade, following alarmingly high ESRD growth rates of ~8% annually, exceeding the 1.3% population growth rate (3). Socioeconomic implications of ESRD are huge as the cost of treatment with renal replacement therapy (RRT) is prohibitive for many developing countries while unsustainable in developed countries. The burden on national resources is further compounded by the high cardiovascular disease (CVD) burden observed in CKD patients (3, 4). In response to the socioeconomic challenges, there has been a worldwide shift towards CKD screening and early diagnosis, particularly in individuals deemed at high risk, following the 2004 call by the International Society of Nephrology for concerted global efforts to reduce the impact of ESRD (5). The need is even more dire in sub-Saharan Africa, where RRT is either absent or only available on a small scale; where available, RRT facilities are in urban centres and the cost varies widely as shown in Table 1.5 (6, 7).

Table 1.5. Cost of haemodialysis versus peritoneal dialysis in some African countries[a] (7)

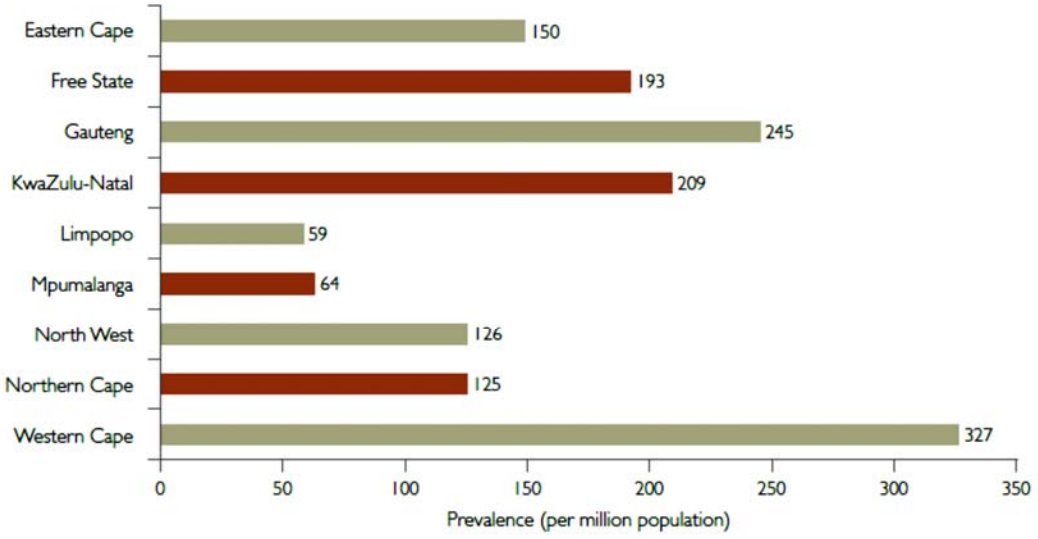
Country	Annual cost per patient (US$)	
	Peritoneal dialysis	Haemodialysis
South Africa	12 000	7 000
Sudan	11 500	10 500
Kenya	12 000	16 000
Senegal	19 500	27 000
Nigeria	25 000–55 000	20 000–49 000
Namibia	24 500	24 500

[a]Figures presented in this table are estimates provided by Sarala Naicker (South Africa), Ahmed Twahir (Kenya), Abdou Niang (Senegal), Felicia Eke (Nigeria), Ebun Bamgboye (Nigeria), and Sr. A. Prins (Namibia) in response to an e-mail-based survey conducted by the authors. Published in Peritoneal Dialysis International. Reprinted with permission from Abu-Aisha H and Elamin S. (7) Peritoneal dialysis in Africa. Perit Dial Int 2010; 30:23–28.

1.1.3. THE RISING BURDEN OF CHRONIC KIDNEY DISEASE IN SOUTH AFRICA

The exponential increase in the ESRD burden has also been reported in South Africa. The 1994 South African Dialysis and Transplant Registry Report (SADTR), had 3399 ESRD patients on RRT, which was equivalent to 99 patients per million population (pmp) (6). Twenty years later in 2014, that figure stood at 178 pmp and the latest annual report from the South African Renal Registry (SARR), which has replaced the SADTR, shows that the number of ESRD patients on RRT further increased to 10 360 in 2015, a prevalence of 189 pmp (8). The report further highlights the socioeconomic disparities in accessing RRT in South Africa as this huge rise in the RRT prevalence is largely due to increased numbers of patients accessing RRT in the private healthcare sector, which only serves 16% of the population, and is observed across all the 9 provinces of the country (Figure 1). The RRT prevalence in the public sector, which is responsible for healthcare for the majority of the South African population (84%), has remained unchanged at 71.9 pmp (8). These data underscore the need for research into CKD to elucidate potential areas of intervention that can reduce the impact of CKD in our population.

Figure 1. Prevalence and numbers of patients on RRT by province (8).



Province	EC	FS	GT	KZN	LP	MP	NW	NC	WC	All
Patients	1 040	544	3 238	2 286	337	273	466	148	2 028	10 360

Reprinted from Davids MR, Marais N, Jacobs JC. (8) South African Renal Registry Annual Report 2015. African Journal of Nephrology 2017; 20 (1):201-213. Accessed at http://dx.doi.org/10.21807/20-1-2583 under a Creative Commons licence - http://creativecommons.org/licenses/by-nc-nd/4.0/

1.2. LITERATURE REVIEW

1.2.1. RISK FACTORS FOR DEVELOPMENT OF CHRONIC KIDNEY DISEASE

1.2.1.1. Diabetic and hypertensive nephropathies

Diabetic nephropathy is the cause of ESRD in up to 40% of patients starting RRT globally (9) while hypertension is the leading cause in sub-Saharan Africa, accounting for 25–50% of patients starting RRT (10). In the 2015 SARR Annual Report, 33.7% patients had hypertensive renal disease listed as the cause of ESRD while diabetic nephropathy was reported in 14.4% (8). These data, based on treated ESRD, probably underestimate the ESRD burden in South Africa because >50% of patients assessed for RRT in public healthcare facilities were unlikely to be accepted due to stringent selection criteria and rationing of RRT (11) hence the need for data in untreated ESRD and pre-ESRD.

1.2.1.2. Human immunodeficiency virus and other infection-related glomerulopathies

Glomerulonephritis was reported in 16–52% of ESRD in sub-Saharan Africa, with infections such as human immunodeficiency virus (HIV), hepatitis B virus (HBV) and malaria endemic in the region (12, 13). However, HBV- and malaria-associated glomerulopathies have become uncommon in some parts owing to interventions, like hepatitis B vaccination, improved living standards as well as access to healthcare (14, 15). Prevalence of glomerulonephritis (9.5%) was much lower in the 2015 South African Renal Registry Report, than in previous reports; HBV and HIV seroprevalence was 1.3% and 9.4%, respectively (8). HIV inclusion reflects changing practice in South Africa since HIV was not represented in previous ESRD data, because HIV patients were not offered RRT until recently (16). HIV-associated nephropathy (HIVAN) was shown to be the main cause of CKD in HIV in a renal biopsy study done at our institution, where it was found in 83% of HIV patients who underwent renal biopsy for proteinuria and 86% of patients with persistent microalbuminuria (17). Hepatitis C virus (HCV) infection is another known cause of glomerulonephritis, however it has not featured significantly in South Africa and was not shown to cause glomerulonephritis in a study of patients presenting to our hospital in the late 1990s although HIV patients were excluded in that study population (18).

1.2.1.3. Tubulointerstitial diseases

Tubulointerstitial diseases are less common in South Africa and the rest of sub-Saharan Africa. Cystic kidney diseases including autosomal dominant polycystic kidney disease (ADPKD) accounted for 3.3% of ESRD in the 2012 South African Renal Registry data (19). Obstructive uropathy was reported in 5% of ESRD patients in a study from Nigeria and 12% in Sudan (12). Rarer tubulointerstitial diseases may result from renal stones, urinary tract infections, nephrotoxic drugs, systemic infections, autoimmune diseases and malignancies (2).

1.2.1.4. Demographic variables

African and Asian ethnicity are strongly associated with increased susceptibility to CKD in population-based studies (20). The earliest evidence showed a 3.8 times higher risk of ESRD in African Americans than Caucasians (21). Subsequent studies consistently showed higher age- and sex-adjusted ESRD incidence rates in African Americans compared to Caucasian Americans (22). Similarly, non-Caucasian populations in other countries showed significant excess risk of incident ESRD relative to their Caucasian counterparts (23). Age is another well-recognized risk factor, with CKD prevalence shown to rise sharply with age to 23.4–35.8% in persons ≥65 years (population prevalence: 7.2%), as well as female gender (20).

1.2.1.5. Genetic and other risk factors

Ethnic disparities in the ESRD risk lead to research into genetic susceptibility factors. In earlier studies, the myosin-9 gene (*MHY9*) appeared to explain the excess CKD risk with African ancestry, however, subsequent studies identified the neighbouring *APOL1* gene as the main explanation for the associations previously attributed to *MHY9* (24). The *APOL1* gene was recently shown to be strongly associated with HIVAN in black South Africans [OR 89 (18; 912), $p<0.001$, for homozygotes] (25). Other factors associated with increased susceptibility to CKD include low birth weight as well as obesity, which are both also risk factors for hypertension and diabetes, further compounding CKD risk (26).

1.2.2. COMPLICATIONS ASSOCIATED WITH CHRONIC KIDNEY DISEASE

1.2.2.1. Metabolic and endocrine complications of chronic kidney disease

Several disorders occur as a direct consequence of loss of endocrine or exocrine kidney function, notably anaemia, mineral metabolism disorders and metabolic acidosis. These disorders, which have been collectively referred to here as metabolic, are associated with poor renal outcomes in non-dialysis CKD with increased risk of CKD progression observed with anaemia (27, 28), mineral metabolism disorders, particularly higher serum phosphate, calcium-phosphate product, parathyroid hormone (PTH) and fibroblast growth factor-23 (29-31) as well as metabolic acidosis (32-35). Hyperuricaemia is another disorder observed with progressive CKD (36-39) and increasingly, has been associated with development of incident CKD and CKD progression (36, 40, 41).

1.2.2.2. Cardiovascular disease in chronic kidney disease

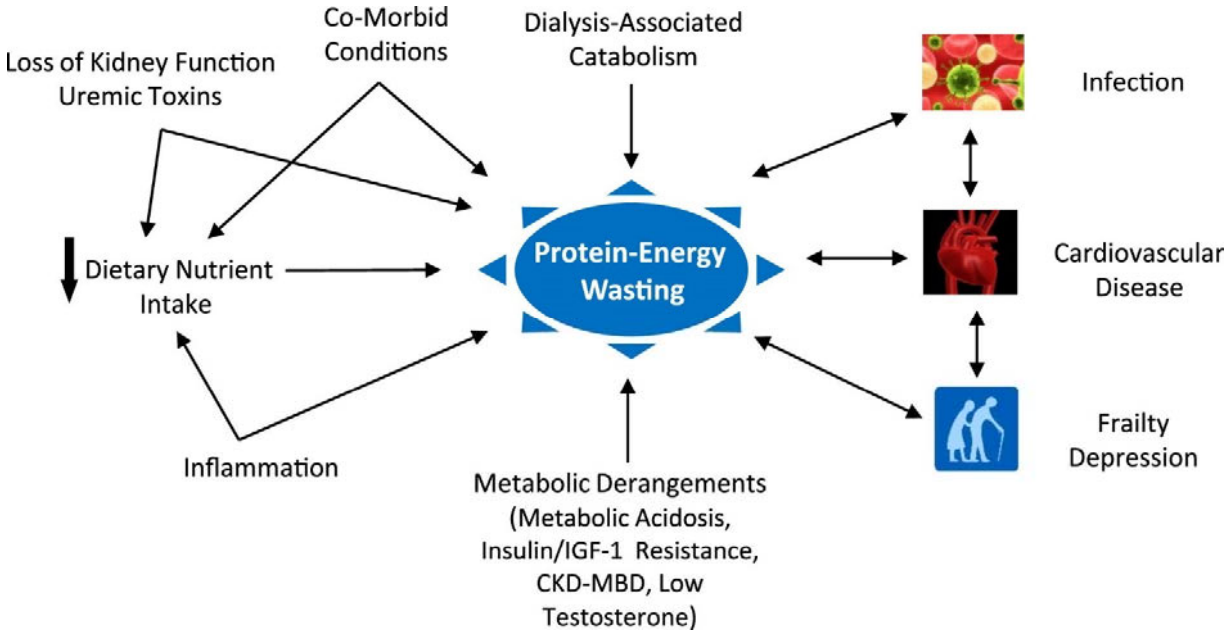
The high CVD prevalence in CKD has been well-documented since initial reports that 30–40% of patients presenting to nephrologists had a history of ischaemic heart disease (IHD) (42, 43). Early studies reported that CVD incidence was 2–3 times higher in predialysis CKD patients than in the general population (44). Later studies showed a 10–30 times increased CVD mortality in CKD than in the general population (4). A comprehensive review of that early evidence was published in the 2003 American Heart Association Scientific Statement, which recommended inclusion of CKD in the highest risk group for CVD risk factor prevention, detection and treatment (4). Although initial data were from dialysis and predialysis patients, recent population studies have reported the association of increased CVD events with worsening eGFR and higher albuminuria, independent of traditional CVD risk factors (45-48). These data provided evidence for including both markers in CKD risk evaluation, definition and staging (2).

The CVD burden in CKD in sub-Saharan Africa is unknown but is probably high as elsewhere. Clinical CVD was observed in >30% of Nigerian patients with diabetic nephropathy, with PVD in 27% and stroke in 4% while none had IHD (49). Studies using left ventricular (LV) hypertrophy as a surrogate for CVD reported a high prevalence of LV hypertrophy and significant association with CKD (49-54). A study of South African haemodialysis (HD) patients reported LV systolic dysfunction in 20.2% and diastolic dysfunction in 65.1% (50). In Ethiopia, CVD was the commonest comorbid disease in a study of HD patients, present in 29.7% (55).

1.2.2.3. Protein energy wasting

Abnormal protein metabolism was first recognized as a CKD complication >40 years ago when studies reported loss of body fat and lean body mass in patients with severe renal failure (56, 57). Subsequent studies consistently reported a high prevalence of protein catabolism, muscle wasting and malnutrition in CKD but wide variation in terminology prompted development of the current definition of protein energy wasting (PEW) (58). While PEW is common in dialysis patients, prevalence in early CKD is also estimated to be higher compared to the general population, increasing as GFR declines (59-61). PEW is associated with increased morbidity and mortality in dialysis as well as predialysis CKD patients, which was mainly related to atherosclerotic CVD (59, 62). A conceptual model of the multiple mechanisms involved in PEW is illustrated in Figure 2. Improved survival has been reported with nutritional interventions, treatment of comorbidities, inflammation, metabolic and hormonal disorders as well as adequate dialysis but randomized controlled trials are lacking (63).

Figure 2. A conceptual model for aetiology of PEW and its direct clinical implications (63)



IGF-1, insulin-like growth factor-1: CKD-MBD, chronic kidney disease- mineral bone disorder; Reprinted from Carrero JJ, Stenvinkel P, Cuppari L. et al. (63) Aetiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr 2013; 23(2): 77-90. Accessed at http://dx.doi.org/10.1053/j.jrn.2013.01.001 under a Creative Commons licence - http://creativecommons.org/licenses/by-nc-nd/4.0/

Diagnostic criteria for PEW (Table 1.6) comprise changes in serum biochemical markers, body mass, muscle mass and dietary intake. Diagnosis requires presence of at least 3 of the 4 categories, with at least 1 test fulfilled in each category.

Table 1.6. Diagnostic criteria for protein energy wasting (58, 59)

Serum chemistry	
Serum albumin	<38 g/l
Serum prealbumin (transthyretin)	<30 g/l (for maintenance dialysis patients only)
Serum cholesterol	<100 mg/dl
Body mass	
Body mass index	<23 kg/m^2 (age ≥65years) or <22 kg/m^2 (age <65 years)
Unintentional weight loss over time	≥5% over 3 months or ≥10% over 6 months
Total body fat percentage	<10%
Muscle mass	
Muscle wasting: reduced muscle mass	≥5% over 3 months or ≥10% over 6 months
Reduced mid-arm muscle circumference area	>10% reduction in relation to 50th percentile of reference population
Creatinine appearance	
Dietary intake	
Unintentional low dietary protein intake	<0.80 g/kg/day for at least 2 months for dialysis patients or <0.6 g/kg/day for patients with stages 2–5 CKD
Unintentional low energy intake	<25 kcal/kg/day for at least 2 months

Reprinted from Kidney Int, vol 73, Fouque D, Kalantar-Zadeh K, Kopple J et al.(58) A proposed nomenclature and diagnostic criteria for protein-energy wasting in acute and chronic kidney disease, pages 391–398, 2008, with permission from Elsevier; accessed at http://dx.doi.org/10.1038/sj.ki.5002585; adaptation from Semin Nephrol, vol 29, Dukkipati R, Kopple J.(59) Causes and prevention of protein-energy wasting in chronic kidney failure, pages 39-49, 2009, with permission from Elsevier; accessed at http://dx.doi.org/10.1016/j.semnephrol.2008.10.006

1.2.3. PREDICTION OF GLOMERULAR FILTRATION RATE

1.2.3.1. Methods to determine glomerular filtration rate

Early detection of CKD requires that GFR can be determined easily and fairly accurately. A number of GFR prediction equations are readily available in clinical practice (64-67), providing a practical alternative to the costly gold standard methods for GFR measurement. The Cockcroft-Gault (CG) equation (64) is difficult to implement in routine laboratories because body weight and height are not usually recorded on laboratory requisitions whereas the Modification of Diet in Renal Disease (MDRD) equation (66) does not require these. Studies consistently showed that CG and MDRD equations were imprecise at high GFR levels (68). This prompted development of the Chronic Kidney Disease in Epidemiology (CKD-EPI) equation, which was shown to be as accurate as the MDRD equation at GFR <60 ml/min/1.73m^2 and more accurate at GFR ≥60 ml/min/1.73m^2 (67).

1.2.3.2. Performance of estimated glomerular filtration rate in different populations

Discrepancies have been observed in the accuracy of eGFR equations in some populations. Studies in Asian populations showed that predictive performance of MDRD-eGFR was poor and improved when a modified coefficient derived in the Chinese and Japanese was included (69, 70). Poor performance of eGFR equations was also found in South Asians (71). Validation studies in sub-Saharan Africa reported poor GFR prediction with CG and with MDRD as well as CKD-EPI equations, which improved when the black ethnicity correction factors were omitted in the latter two (72, 73). These studies highlighted the need for developing a coefficient or equation in a specific population that would be more suitable for that population to improve GFR prediction.

1.3. RATIONALE

There is a paucity of CKD epidemiological data in South Africa. Hypertension, diabetes, obesity and HIV, collectively, pose a significant threat to the national budget as diseases of affluence increase alongside diseases of poverty. Furthermore, CKD is a recognized complication of these disorders and, with the added CVD burden, its socioeconomic implications have the potential to reach catastrophic proportions. Identification of CKD, associated risk factors and complications presents opportunities for implementing primary, secondary and tertiary prevention strategies to reduce the impact of CKD thus improving patient outcomes across the spectrum of CKD. Therefore, an understanding of CKD epidemiology in the local population will provide substantial information necessary in healthcare planning and utilization of limited resources. An important part of the study of the CKD epidemiology is the evaluation of cost-effective diagnostic methods that can be implemented in routine clinical practice hence this formed an important component of the work presented in this thesis.

1.4. HYPOTHESIS

Several hypotheses tested in this research work were that:

1.4.1. Diabetes mellitus as well as HIV had become the commonest contributors to the burden of CKD in the local patient population, exceeding hypertension, in keeping with the emergence of diabetes as the leading cause globally and with the epicentre of the HIV pandemic being in KwaZulu-Natal.

1.4.2. The proportions of patients with advanced CKD (stage ≥3b) and related complications were likely to be high as a consequence of poor control of factors associated with disease progression as well as lack of access to specialized predialysis care by a nephrologist due to a severe shortage of nephrologists.

1.4.3. We also hypothesized that an equation developed in patients of African ancestry would predict GFR more accurately in this population compared to currently used equations that were developed in other populations and that would enable early CKD diagnosis, thus reducing the socioeconomic impact of CKD.

1.5. AIM

To reduce the socioeconomic impact of CKD through determining associated risk factors and complications well as establish a suitable CKD detection method in adults

1.6. OBJECTIVES

The specific objectives have been outlined in each of the manuscripts published or submitted as part of this thesis as listed below:

1.6.1. To describe the spectrum of CKD and CVD risk factors in patients attending a rural outreach CKD clinic (Chapter 2)

1.6.2. To describe the spectrum of CKD and CVD risk factors in an urban hospital setting and prevalence of elevated serum urate as a potential therapeutic target for CKD (Chapter 3)

1.6.3. To describe the prevalence, severity and predictive factors of CKD-related metabolic complications across the spectrum of CKD (Chapter 4)

1.6.4. To determine body composition and other components of the PEW syndrome in patients with non-dialysis dependent CKD as well as assess the relationship with GFR (Chapter 5)

1.6.5. To evaluate the predictive performance of various GFR prediction equations against technicium-99m-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) imaging (Chapter 6)

1.6.6. To develop a simple cost-effective method for estimating GFR that is suitable for black South Africans (Chapter 7)

1.7. GENERAL METHODOLOGY

The work comprises a combination of observational studies undertaken at 2 major hospitals located in 2 of 3 regions in the province of KwaZulu-Natal; Area 1 is composed of the Ethekwini metro as well as districts of Ugu and Ilembe while area 3 comprises Uthungulu, Zululand and Umkhanyakude districts. Details of study participants, setting and methods are fully stated in each study included in the chapters of the thesis.

CHAPTER 2

CHARACTERISTICS OF SOUTH AFRICAN PATIENTS PRESENTING WITH KIDNEY DISEASE IN RURAL KWAZULU-NATAL: A CROSS SECTIONAL STUDY

Madala, N. D., Thusi, G. P., Assounga, A. G., & Naicker, S. (2014). Characteristics of South African patients presenting with kidney disease in rural KwaZulu-Natal: a cross sectional study. BMC Nephrol. 15(1), 61.

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Characteristics of South African patients presenting with kidney disease in rural KwaZulu-Natal: a cross sectional study

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Abstract

Background: Diabetes mellitus is the leading cause of end stage renal disease (ESRD) globally. Diabetes and human immunodeficiency virus (HIV), both prevalent in South Africa, have not been reported as significant causes of ESRD.

Methods: We evaluated chronic kidney disease (CKD) and cardiovascular disease risk factors in a cross sectional study of 302 patients (165 females/ 137 males) at a CKD clinic in rural northern KwaZulu Natal. We included all CKD outpatient clinic attendees and excluded acute renal failure patients. Demographic, clinical and laboratory data collected were analyzed with Stata11 software. Logistic regression analysis was used to determine factors associated with advanced CKD and results expressed as the odds ratio with the 95% confidence interval [OR (95% CI)].

Results: Of 302 patients analyzed, 290 (96%) were black African. Mean age ± SD was 47.1 ± 17.0 years. Approximately 86.4% of females and 54.5% of males were overweight/ obese. Dyslipidaemia was observed in 47.9% females and 29.2% males (P < 0.001). Estimated glomerular filtration rate (eGFR) was <30 ml/min/1.73 m^2 in 50.6% patients. CKD risk factors observed were: hypertension (77.8%), diabetes (29.8%), HIV (28.5%), glomerulonephritis (7.0%) and tubulointerstitial diseases (5.6%). Independent factors associated with eGFR <30 ml/min/1.73 m^2 at presentation were: HIV [OR = 2.4 (1.3 4.2), P = 0.004] and hypertension [OR = 2.3 (1.3 4.2), P = 0.007].

Conclusion: Diabetes and HIV are prevalent in CKD patients at primary/regional level healthcare in South Africa. With registry data lacking, dedicated CKD clinics at lower healthcare levels may provide valuable data on CKD epidemiology including changes in aetiology. Primary healthcare practitioners are faced with advanced CKD patients in resource poor settings, with limited opportunity for upward referral hence the need for nephrology outreach programs.

Keywords: Chronic kidney disease, Diabetes, Dyslipidaemia, HIV, Hypertension, Rural, South Africans

Background

Hypertension and glomerulonephritis were the major causes of end-stage renal disease (ESRD) among South Africans in previous registry data [1]. In contrast, data have shown type 2 diabetes as the commonest cause of ESRD globally, accounting for up to 40% [2]. This has been in parallel with the global increase in the prevalence of obesity and type 2 diabetes. The prevalence of obesity and diabetes in South Africa has been reported to be high [3]. Data have also shown that mortality from diabetes increased by 38% in the period from 1999 to 2006 with an even greater increase of 67% reported for mortality due to kidney diseases [4]. Diabetic patients have been under-represented in registry data hence accurate data on the prevalence of diabetes in the South African ESRD population are lacking. A study in the Western Cape province reported that <20% of diabetic patients assessed for renal replacement therapy (RRT) between 1988 and 2003 were offered RRT, consequently diabetic patients only comprised 6.2% of accepted patients overall [5].

Human immunodeficiency virus (HIV) infection is another ESRD cause under-represented in local data since HIV patients were previously excluded from RRT and

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are only recently being offered RRT. [6] The socioeconomic and health consequences of CKD are well-documented globally [7,8]. Apart from the high costs of RRT, the pressure on national resources is further compounded by the high cardiovascular disease (CVD) burden observed in CKD patients. Consequently, concerted global efforts aimed at CKD screening and early diagnosis have been called for [9]. Screening of the general population for CKD has not been considered cost-effective hence many CKD screening programs often target individuals and groups characterized by a high CKD prevalence [10]. Variable success rates have been reported from countries worldwide, including South Africa, with the best prospects for sustainability observed in programs that could be incorporated into national health policy [11,12]. Therefore, epidemiological data are needed in South Africa to provide the necessary framework for incorporating CKD early detection and management into primary level healthcare with other chronic non-communicable diseases. Our aim was to describe the prevalence of CKD and CVD risk factors and determine factors associated with CKD severity in patients presenting at a CKD clinic in the predominantly rural northern KwaZulu-Natal region, South Africa.

Methods

Study design and setting

This was a cross-sectional analysis of records kept at the clinic of consecutive outpatients seen at the dedicated CKD clinic at Ngwelezana hospital situated in the Uthungulu district, 5 km from the town of Empangeni and approximately 200 km north of Durban, in KwaZulu-Natal province, South Africa. The hospital provides district (primary) level and regional (secondary) level healthcare services to 20 district hospitals that provide primary healthcare services to the approximately 2 million people living in the northern KwaZulu-Natal districts of Uthungulu, Zululand as well as Umkhanyakude. The majority live in rural areas with the proportion of the population living in urban areas estimated at 14.5%, 13.4% and 3.8%, for Uthungulu, Zululand and Umkhanyakude, respectively [13]. The region is largely poorly-resourced with the latter 2 ranked among the 10 most deprived districts in South Africa in 2007 [14]. Only acute peritoneal dialysis through a rigid catheter was offered at Ngwelezana hospital and only a minority of patients could access RRT in the academic tertiary level nephrology unit in Durban. The clinic, established by a specialist physician in 2008 to improve early CKD identification, had junior doctors, nurses, a social worker, dietician and visiting nephrologist weekly initially, with less frequent visits later. The University of KwaZulu-Natal Biomedical Research Ethics Committee approved the study.

Patients

We reviewed records, kept at the CKD clinic, of all patients seen from 31st January 2008 to 31st January 2011. All patients presenting to the clinic were referred by primary healthcare doctors from any of the 20 district hospitals in the geographic area served by the hospital. Referral was at the discretion of the primary healthcare doctor and each patient presented with a referral letter from the referring doctor providing details of the clinical diagnosis made, results of investigations performed at the referring hospital as well as their current medication. All referrals to our clinic were for kidney disease based on clinical as well as structural evidence of kidney disease noted at the referring hospital, including proteinuria and elevated serum creatinine levels. At first presentation to our clinic, all patients underwent clinical assessment (history and examination) and laboratory investigations were done as part of standard care. Renal disease aetiology was largely determined clinically as renal histology was unavailable except where glomerulonephritis unrelated to HIV was suspected and those patients were referred to the tertiary center in Durban for a renal biopsy. Renal ultrasound services were available intermittently and were accessed when that was feasible.

Inclusion criteria were: Patients with a diagnosis of CKD

Exclusion criteria were: Diagnosis of acute renal failure

Data collection

The following data were recorded for each patient.

a. *Demographic characteristics*: Age, gender, ethnicity, source of referral, area of residence and smoking status, where ethnicity was used according to Census population classification data: African (black), white, Indian and coloured [13]. Referral source was categorized according to location of the referring hospital into: (i) Uthungulu district, in which the CKD clinic was located, (ii) Umkhanyakude and (iii) Zululand. Patients were classified as urban or rural based on Census definitions of their place of residence [13]. Smoking was recorded as (i) never smoked/ex-smoker and (ii) current smoker.
b. *History*: Medical history, such as hypertension, diabetes, HIV, dyslipidaemia and medication. Patient records, referral documents, current medication and pharmacy entries were used in conjunction with self-reported history to establish the diagnosis.
c. *Physical examination*: Anthropometric measures [weight (kg), height (cm), waist circumference (cm) and body mass index = weight/height^2 (kg/m^2)], blood pressure (mmHg) and dipstick analysis for proteinuria. Overweight/obese was defined as

presence of BMI ≥25 kg/m^2 and/or waist circumference ≥80 cm in females and ≥92 cm in males.

d. *Laboratory tests*: Results of blood tests recorded were - serum creatinine, total cholesterol, serum albumin and haemoglobin. Total cholesterol >5.0 mmol/l was included in dyslipidaemia definition. Serum creatinine results were obtained prior to the implementation of the IDMS-traceable assay and values were not recalibrated to be IDMS-traceable. The abbreviated Modification of Diet in Renal Disease (MDRD) and Schwartz equations were used to calculate eGFR in patients aged ≥18 years and <18 years, respectively:
   1. MDRD-eGFR (mL/min/1.73 m^2) = $186 \times (\text{Serum creatinine}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if African American})$ [15]
   2. Schwartz - eGFR (mL/min/1.73 m^2) = k x (height in cm) ÷ Serum creatinine [16]

The African-American coefficient was omitted following evidence that this improved MDRD-eGFR equation accuracy in Africans [17-19].

Definitions

CKD was defined by eGFR <60 ml/min/1.73 m^2 and/or proteinuria and/or abnormal renal ultrasound, persistent for ≥3 months.

Acute renal failure was defined by complete recovery of kidney function on subsequent visits after initial presentation.

Statistical analysis

Intercooled Stata version 11 (Texas, USA) was used for data analysis. Categorical data were described as proportions and males compared with females using the chi-square test. Continuous data were summarized as mean ± standard deviation (SD) with the t-test used to assess differences between males and females. Non-normal data were expressed as median (interquartile range) and differences between the two groups were evaluated using the Mann–Whitney test. Odds ratios (95% CI) were calculated using logistic regression analysis to evaluate the factors associated with presenting with a low eGFR (<60- and <30 ml/min/1.73 m^2).

Results

A total of 313 CKD patients, 174 (55.6%) females and 139 (44.4%) males, were seen on their first visit during the study period (mean age 47.1 ± 17.0 years). Data were available for 302/313 (96.5%) patients that were included in the analysis and 11 patients were excluded due to unavailability of clinical and/or laboratory data. The ethnic distribution of study patients was: 290/302 (96%) African (black), 4 (1.3%) Indian and 8 (2.7%) white. This closely resembled the population distribution in the 3 districts comprising northern KwaZulu-Natal [13]. Almost two-thirds, 191 (63.3%) were referred from Uthungulu district while 85 (28.2%) and 26 (8.6%) were from various hospitals across Umkhanyakude and Zululand districts, respectively. Over half, 165 (54.6%) were classified as urban and 137 (45.4%) as rural. Table 1 shows clinical and laboratory characteristics at presentation by gender. Significantly more males than females reported current smoking while females were more likely than males to have the CVD risk markers of being overweight/obese and having dyslipidaemia. Over 70% presented with stage 3 CKD or worse with the presenting median eGFR (IQR) being 28.9 (49.8) ml/min/1.73 m^2.

Aetiology of CKD and co-morbid risk factors

Figure 1 shows that the 3 commonest diagnoses encountered were: hypertension in 227 (75.2%), diabetes in 90 (29.8%) and HIV in 86 (28.5%) with similar gender distribution. Self-reported history was verified in all patients using medical records. Renal diagnoses in 21 patients referred for renal biopsy were: primary glomerulonephritis (16), hepatitis B virus-associated (4) and lupus nephritis (1). Tubulointerstitial diseases were observed in 17 (5.6%) with autosomal dominant polycystic kidney disease (11), obstructive uropathy (5) and presumed analgesic nephropathy (1). Hypertension and diabetes increased with age while HIV was prevalent in young patients (Figure 2). Multiple concomitant CKD risk factors were common (51.1%); dual co-morbidities in 136 (47.9%) patients and triple co-morbidities in 9 (3.2%). CKD was attributed to a single cause in 139 (48.9%) patients; 87/302 (28.8%) had hypertension alone, 32/302 (10.6%) had HIV alone while glomerulonephritis alone and tubulointerstitial disease were uncommon; 9/302 (3.0%) and 5/302 (1.7%), respectively (Figure 3). Only 6/90 (6.7%) diabetic patients had diabetes alone with concurrent hypertension in 76 (84.4%) and concurrent HIV in 8 (8.9%). Hypertension was a co-morbid diagnosis in >50% of patients with HIV, glomerulonephritis and tubulointerstitial disease as well (Figure 3).

Other cardiovascular disease risk factors

Dyslipidaemia was found in 118 (39.1%) patients overall and there was no difference in the various CKD stages (P = 0.637). In 226 patients with available data to determine overweight/obese status, prevalence of dyslipidaemia was 44.2% in overweight/obese patients and 28.6% in those who were not, P = 0.032. Fifteen patients (6 males and 9 females) had CVD complications; stroke (8), congestive cardiac failure (6) and atherosclerotic renovascular disease (1).

Table 1 Distribution of demographic, clinical and laboratory data of study patients by gender

Parameter	Male *n = 137*	Female *n = 165*	P value
African	130 (94.9%)	160 (97.0%)	0.282
Rural	60 (43.8%)	77 (46.7%)	0.618
Smoking#	24/134 (17.9%)	2/158 (1.4%)	<0.001
Age (years)	45.0 ± 17.6	48.5 ± 16.8	0.055
Systolic blood pressure (mmHg)	144.6 ± 28.3	141.1 ± 25.5	0.362
Diastolic blood pressure (mmHg)	84.2 ± 18.1	81.0 ± 19.0	0.153
BMI (kg/m^2)#	25.4 ± 5.5	29.4 ± 7.9	<0.001
Waist circumference (cm)#	92.5 ± 15.2	98.5 ± 20.6	0.021
Overweight/obese#	55/101 (54.5%)	108/125 (86.4%)	<0.001
(*% with data*)	(*73.7*)	(*75.8*)	
Dyslipidaemia	40 (29.2%)	78 (47.9%)	0.001
Total cholesterol (mmol/l)*	4.1 (3.5 5.1)	4.5 (3.7 6.0)	0.009
Serum creatinine (μmol/l)*	215 (116 464)	173 (90 336)	0.009
MDRD eGFR (ml/min/1.73 m^2)*	28.5 (11.8 61.9)	30.4 (13.7 63.5)	0.906
% with MDRD eGFR <60	100 (73.0%)	119 (72.6%)	0.933
% with MDRD eGFR <30	68 (49.6%)	85 (51.5%)	0.745
% with MDRD eGFR <15	44 (31.9%)	49 (29.9%)	0.707
Proteinuria	66 (48.2%)	68 (41.2%)	0.225
Serum albumin (g/l)	30.6 ± 9.6	31.3 ± 8.8	0.530
Haemoglobin (g/dl)	10.7 ± 2.7	10.3 ± 2.4	0.183

#Variables with incomplete data; the proportions with available data for smoking, BMI and waist circumference were 97.8%, 54% and 66.4%, respectively, for males while for females data were available in 95.8%, 59.4% and 67.9%, respectively.
Continuous data were summarized as mean ± SD and non normal data* as median (IQR); the 25th 75th percentiles are specified rather than the range. Categorical data were expressed as number (%).

Factors associated with presenting with advanced CKD

Figure 4 shows that eGFR was highest in younger patients and decreased with increasing age [OR = 0.48 (0.37-0.62) per 10-year, P <0.001] but there was no significant age difference in those presenting with eGFR <15 ml/min/1.73 m^2 (P = 0.099). Using logistic regression analysis, independent factors associated with eGFR <60 ml/min/1.73 m^2 at presentation were: age ≥60 years [OR = 4.5 (2.0-10.5)], HIV infection [OR = 3.0 (1.5-5.9], hypertension [OR = 2.7 (1.4-5.0] and rural residence [OR = 1.9 (1.1-3.4)] while a lower presenting eGFR <30 ml/min/1.73 m^2 was strongly associated with HIV as well as hypertension but not with age or residence (Table 2). Disease severity at presentation was not significantly associated with gender, diabetes or referral source.

Discussion

This is the first study in South Africa to report high prevalence estimates for diabetes and HIV, 29.8% and 28.5%, respectively in a single patient cohort at a secondary level healthcare-based dedicated CKD clinic. Our observations add important data on CKD epidemiology outside of a tertiary level nephrology environment, particularly because diabetes and HIV have mostly been under-represented in previous studies. In two recent studies, diabetes was observed in 10.8% of patients in the Free State province and <5% of renal biopsies in the Western Cape province while HIV-associated nephropathy (HIVAN) was high in the latter study, comprising 25.7% of annual renal biopsies in 2009 [20,21]. Most HIV patients in the present study were presumed to have HIVAN since renal biopsy was largely not accessible, which was based on a previous study from our institution that showed HIVAN in >80% of HIV patients with microalbuminuria or overt proteinuria [22].

Dedicated CKD clinics typically conducted at tertiary level by nephrologists were inaccessible to most patients in this study due to various healthcare resource constraints hence the establishment of this CKD outreach clinic. Published South African experience of nephrology outreach is limited to a study in Soweto primary healthcare clinics in Gauteng province that found eGFR <60 ml/min/1.73 m^2 in 26% and nephrotic-range proteinuria in 9% of patients evaluated [12]. The high proportion of patients with advanced disease (50.6% with eGFR <30 ml/min/1.73 m^2) in our clinic highlights an important reality in resource-poor settings that CKD

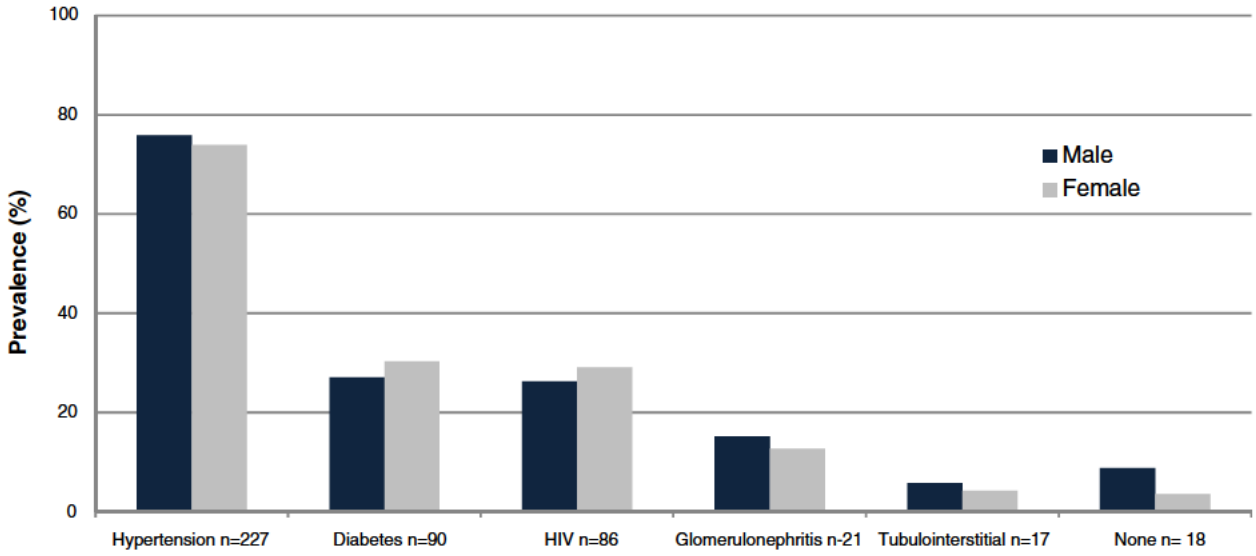

Figure 1 Prevalence of CKD risk factors in the 302 study patients.

patients remain at district and regional level healthcare unable to access tertiary care, thus primary healthcare practitioners are managing increasingly complex patients.

The strong association of HIV and hypertension with a low presenting eGFR level in this study may be due to late referral or it may suggest a high risk for CKD progression in this population. In a recent systematic review, independent risk factors for late referral in CKD included older age, multiple comorbidities, renal disease aetiology and lower socioeconomic status [23]. Older age and rural residence (an indicator of poor socioeconomic status) were independent factors associated with presenting with stage 3 CKD or worse in our study. Only 45% of clinic patients were classified as rural while over 85% of the 2 million population served by our hospital were rural. The discrepancy may be because >60% of referrals were from within the district where the CKD clinic is located, which might suggest disproportionately greater access to the clinic by the urban minority population or a higher CKD prevalence in urban communities; both postulates need further evaluation in population-based studies. The strong association observed between older age and lower eGFR remained significant even after adjusting for hypertension and diabetes, both of which increased in prevalence with age. Hypertension prevalence also increases with worsening CKD, which was also observed in the present study with hypertension found in 80.5% in patients with stage 3 CKD and 85% of those with stage 5 CKD. These findings were in keeping with observations in the Kidney Early

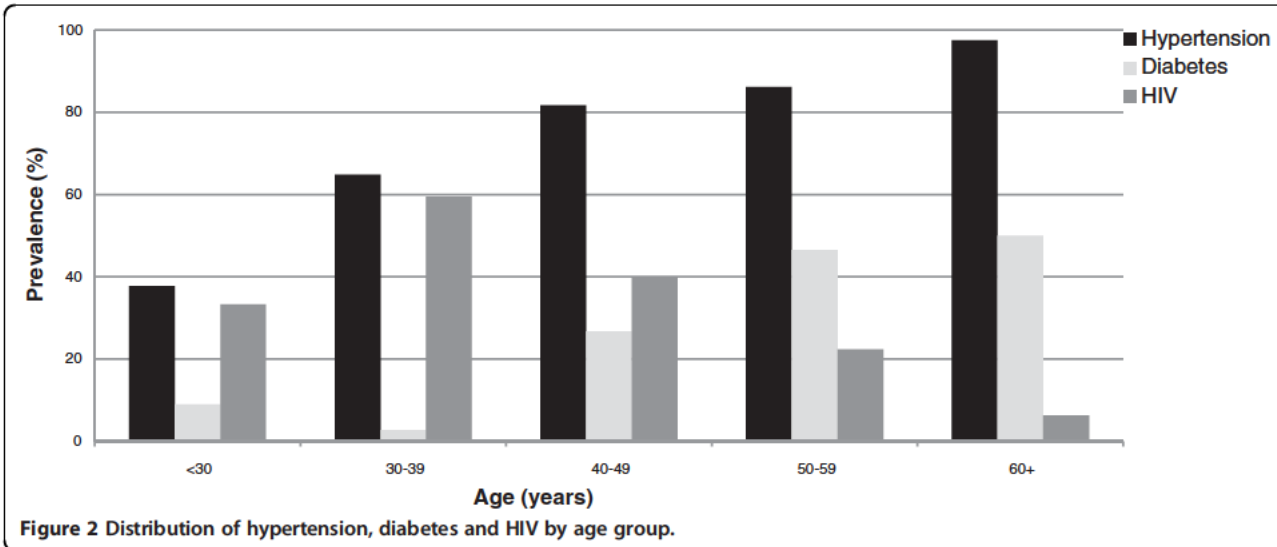

Figure 2 Distribution of hypertension, diabetes and HIV by age group.

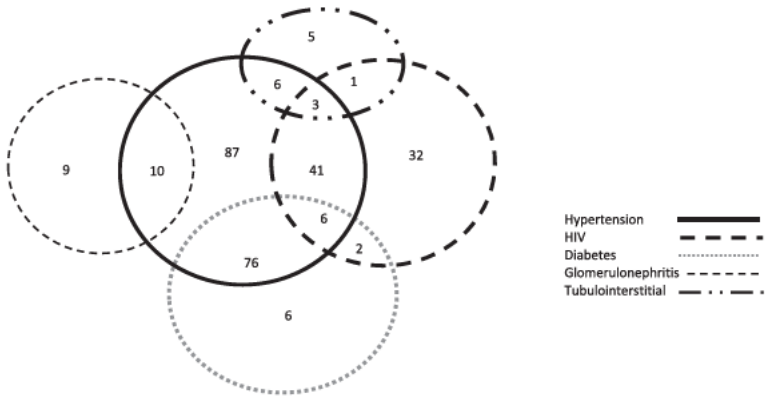

Figure 3 Distribution and overlap of major CKD risk factors in patients with one or more co morbidities.

Evaluation Program in Americans where hypertension prevalence was 86.8% in stage 3 CKD, increasing to 95.5% in stages 4–5 [24].

The high prevalence of advanced CKD in the our study could reflect rapid CKD progression as patients were almost exclusively black (96%) thus at high risk for more severe hypertensive target organ damage, including CKD, as reported in black South Africans [25]. However, CKD progression could not be evaluated in this present study design. Hypertension alone was again shown in this study as the commonest cause of CKD, as in many other studies in black South Africans and other sub-Saharan populations [20,26-29]. Although clinical diagnosis was adopted in this study, there is evidence from published biopsy data for hypertensive nephrosclerosis as the major ESRD cause in black South Africans [26]. Studies in African-Americans showed that African ancestry (black race) is also associated with aggressive CKD in HIV patients. HIV infection in black patients was associated with a greater risk for incident CKD, higher prevalence for more aggressive disease with faster progression to ESRD and worse CKD outcome than in white patients [30]. Studies are needed in South Africans to evaluate progression of CKD in HIV patients, particularly as CKD patients with HIV were younger (mean age 39.5 ± 11.9 years in HIV patients versus 47.1 ± 17.0 years in the overall cohort). The weak association of diabetes with CKD observed in the present study contrasts with the overwhelming evidence in the literature and was probably because too few patients (<10%) had diabetes alone. This could reflect under-recognition or lack of referral of patients with diabetic CKD without concurrent hypertension but there are no published studies in this region to support this speculation thus far. Elsewhere,

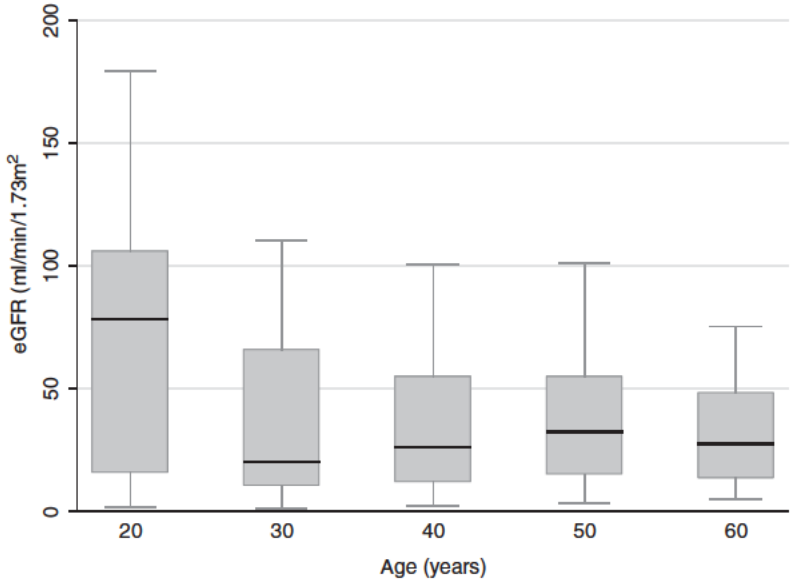

Figure 4 Distribution of patients grouped according to presenting eGFR level and age. The box and whisker plot shows the 25th, 50th and 75th percentiles in various age groups.

Table 2 Multivariable logistic regression analysis results showing factors associated with presenting eGFR <60 and <30 ml/min/1.73 m^2

Risk factor	MDRD eGFR <60		MDRD eGFR <30	
	Adjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Age ≥60 years	4.5 (2.0 10.5)	<0.001	1.4 (0.8 2.5)	0.261
HIV	3.0 (1.5 5.9)	0.001	2.4 (1.3 4.2)	0.004
Hypertension	2.7 (1.4 5.0)	0.002	2.3 (1.3 4.2)	0.007
Rural	1.9 (1.1 3.4)	0.021	1.5 (0.9 2.4)	0.100
Diabetes	1.7 (0.8 3.3)	0.148	1.3 (0.7 2.2)	0.415
Male gender	1.2 (0.7 2.1)	0.493	1.0 (0.6 1.6)	0.998
Referral source	1.3 (0.9 1.8)	0.131	1.2 (0.9 1.5)	0.274

under-recognition of diabetic CKD has been identified as a barrier yet to be overcome in the global efforts against CKD, with some surveys in the United States putting patient awareness of their disease as low as 9.4% in those with diabetic CKD [2]. Patients with suspected glomerulonephritis (non-HIV) in our province tend to be referred directly to the tertiary centre hence the low prevalence in this study differs from previous reports of glomerulonephritis as a common cause of CKD in sub-Saharan Africa [1,5,27,29,31].

The proportion of patients that were overweight/obese in this study (86.4% in females and 54.5% in males) was substantially higher than the reported prevalence of 58.5% and 25.4% in black South African women and men, respectively, in the general population [3]. Our observations were similar to findings in the Soweto study cited earlier, which reported that 86% of females and 40.9% of males were overweight/obese using waist circumference while prevalence was 83% and 75%, respectively, when using a composite measure of waist circumference combined with BMI [12]. Our study is the first to report a high prevalence of dyslipidaemia (39.1%) in South African CKD patients. The results are in keeping with the prevalence of dyslipidaemia or hypercholesterolaemia of 38.4% in sub-Saharan Africa reported in a recent meta-analysis of 16 studies of high cardiovascular-risk patients [32]. However, using total cholesterol to evaluate dyslipidaemia, as in our clinic, may underestimate the true burden since HDL, triglycerides and apolipoproteins are the major abnormalities found in CKD [33].

Study strengths and limitations

This study provides important insight into CKD and CVD risk factors in this population that has not been studied before. The results add to the much needed CKD epidemiology data in South Africa in the absence of RRT registry data and representative population studies. The study is subject to the inherent limitation of a cross sectional design in which causal associations cannot be determined between CKD severity and the various risk factors as the temporal sequence is unknown. Selection bias may have potentially occurred from preferential referral of advanced CKD patients over those with earlier CKD and contributed to the small sample size thus results may not reflect the true prevalence in northern KwaZulu-Natal. Another limitation is the use of serum creatinine values without re-calibration to the IDMS assay as this could have introduced bias in calculating eGFR. Correction to the IDMS method substantially improves accuracy of MDRD-eGFR, especially in CKD stages 1–3 although the impact of correction was shown to be minimal at GFR <45 ml/min/1.73m^2 [34]. We expect the bias from non-standardized creatinine to be small in this study, as the median eGFR was low. This will be eliminated in future studies as all laboratories nationally now use standardized serum creatinine in calculating eGFR. The validity of MDRD eGFR in HIV patients is uncertain thus using MDRD eGFR in our HIV patients may be a potential limitation. There are no validation studies in our population and data from published validation studies in various populations are inconclusive on the equation that provides the best GFR estimate. A recent systematic review of studies that evaluated MDRD eGFR reported that the performance was similar in HIV-infected and HIV-negative patients [35]. The absence of renal histology, CD4 cell count and antiretroviral (ARV) therapy data may also be a limitation since these may be significant risk factors for incident CKD as well as progression.

Study implications

The implications of our findings of advanced CKD in the majority (>70%) of patients, in strong association with HIV infection and hypertension, is that patients presenting with these conditions should be screened for CKD at initial presentation to primary healthcare practitioners and regularly thereafter. The high HIV burden in South Africa as well as the widespread national ARV therapy roll-out program with the resultant improving

patient survival means that HIV is likely to become a significant contributor to the CKD burden. Further research is needed to determine the public health impact including resource requirements for CKD early detection and management. The successful integration of HIV care into the primary healthcare system nationally, even in resource-poor settings, provides a promising model for CKD as well, hence integration of CKD screening and management into the existing HIV infrastructure needs to be explored as a potentially feasible strategy in managing CKD.

Conclusion

Our results provide evidence for the first time in South Africa that diabetes and HIV are prevalent in CKD patients at primary/regional level suggesting that both may be emerging as significant causes of CKD in South Africans, following hypertension. The high prevalence of advanced CKD and other CVD risk factors in this cohort suggests that increasingly complex patients are being managed at lower healthcare levels in this region, a trend we expect to be more widespread in the country because nephrology services are available only in a few cities. This underscores the need for dedicated CKD clinics with specialist outreach support in resource-poor areas where options for upwards referral and RRT are limited.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

NDM conceived the study while working as the visiting nephrologist, participated in writing the protocol, data collection and interpretation as well as in writing the draft manuscript. GPT conceptualized and established the clinic in 2008 while working as a specialist physician, participated in data collection and in writing the draft manuscript. AGHA provided training for GPT during establishment of the clinic and provided intellectual input in writing the study protocol as well as the manuscript. SN provided critical intellectual input into the study protocol and in revising the draft manuscript. All authors read and approved the final manuscript, except GPT.

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References

1. Naicker S: **End stage renal disease in sub Saharan and South Africa.** *Kidney Int* 2003, **63**(Suppl 83):119 122.
2. Atkins RC, Zimmet P: **Diabetic kidney disease: act now or pay later.** *Acta Diabetol* 2010, **47:**1 4.
3. Puoane T, Steyn K, Bradshaw D, Laubscher R, Fourie J, Lambert V, Mbananga N: **Obesity in South Africa: the South African demographic and health survey.** *Obes Res* 2002, **10**(10):1038 1048.
4. Mayosi BM, Flisher AJ, Lalloo UG, Sitas F, Tollman SM, Bradshaw D: **The burden of non communicable diseases in South Africa.** *Lancet* 2009, **374:**934 947.
5. Moosa MR, Kidd M: **The dangers of rationing dialysis treatment: the dilemma facing a developing country.** *Kidney Int* 2006, **70**(6):1107 1114.
6. South African Renal Society, South African Transplant Society, Southern African HIV Clinicians Society: **Guidelines for renal replacement therapy in HIV infected individuals in South Africa.** *S Afr J HIV Med* 2008, **9**(2):34 42.
7. Weiner DE: **Public health consequences of chronic kidney disease.** *Clin Pharmacol Ther* 2009, **86**(5):566 569.
8. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, McCullough PA, Kasiske BL, Kelepouris E, Klag MJ, Parfrey P, Pfeffer M, Raij L, Spinosa DJ, Wilson PW, American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Cardiology Clinical, and Epidemiology and Prevention: **Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology and Epidemiology and Prevention.** *Circulation* 2003, **108:**2154 2169.
9. Dirks JH, De Zeeuw D, Agarwal SK, Atkins RC, Correa Rotter R, D'Amico G, Bennett PH, El Nahas M, Valdes RH, Kaseje D, Katz IJ, Naicker S, Rodriguez Iturbe B, Schieppati A, Shaheen F, Sitthi Amorn C, Solez K, Viberti G, Remuzzi G, Weening JJ, International Society of Nephrology Commission for the Global Advancement of Nephrology Study Group 2004: **Prevention of chronic kidney and vascular disease: toward global health equity The Bellagio 2004 Declaration.** *Kidney Int* 2005, **68**(Suppl 98):S1 S6.
10. Hallan SI, Stevens P: **Screening for chronic kidney disease: which strategy?** *J Nephrol* 2010, **23**(02):147 155.
11. Smith JM, Mott SA, Hoy WE, International Federation of Kidney Foundations: **Status of chronic kidney disease prevention programs: international Federation of Kidney Foundation Members 2005/2007.** *Kidney Int* 2008, **74**(12):1516 1525.
12. Katz I, Schneider H, Shezi Z, Mdleleni G, Gerntholtz T, Butler O, Manderson L, Naicker S: **Managing type 2 diabetes in Soweto The South African chronic disease outreach program experience.** *Prim Care Diabetes* 2009, **3**(3):157 164.
13. Statistics South Africa: **Provincial profile KwaZulu Natal. Report No. 00 91 052004.** In http://www.statssa.gov.za/publications/Report 00 91 05/Report 00 91 052004.pdf (Accessed 21st January 2014).
14. Monticelli F, Day C, Barron P: **District health baromater 2007/2008. Indicator comparisons by district: socio economic indicators.** In http://www.hst.org.za/uploads/files/dhb0708 sec1.pdf (Accessed 29th January 2013).
15. Levey AS, Stevens LA, Schmid CH: **A new equation to estimate glomerular filtration rate.** *Ann Intern Med* 2009, **150**(9):604 612.
16. Schwartz GJ, Haycock GB, Edelman CM, Spitzer A: **A simple estimation of glomerular filtration rate in children derived from body weight and plasma creatinine.** *Pediatrics* 1976, **58:**259 263.
17. Van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ: **Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft Gault equations.** *Clin Chemistry* 2008, **54**(7):1197 1202.
18. Eastwood JB, Kerry SM, Plange Rhule J, Micah FB, Antwi S, Boa FG, Banerjee D, Emmett L, Miller MA, Cappuccio FP: **Assessment of GFR by four methods in adults in Ashanti, Ghana: the need for an eGFR equation for lean African populations.** *Nephrol Dial Transplant* 2010, **25**(7):2178 2187.
19. Madala ND, Nkwanyana N, Dubula T, Naiker IP: **Predictive performance of eGFR equations in South Africans of African and Indian ancestry compared with (99 m)Tc DTPA imaging.** *Int Urol Nephrol* 2012, **44**(3):847 855.
20. van Rensburg BW, van Staden AM, Rossouw GJ, Joubert G: **The profile of adult nephrology patients admitted to the Renal Unit of the Universitas Tertiary Hospital in Bloemfontein, South Africa from 1997 to 2006.** *Nephrol Dial Transplant* 2010, **25**(3):820 824.

21. Okpechi I, Swanepoel C, Duffield M, Mahala B, Wearne N, Alagbe S, Barday Z, Arendse C, Rayner B: **Patterns of renal disease in Cape Town South Africa: a 10 year review of a single centre renal biopsy database.** *Nephrol Dial Transplant* 2011, **26**(6):1853 1861.
22. Han TM, Naicker S, Ramdial PK, Assounga AGH: **A cross sectional study of HIV seropositive patients with varying degrees of proteinuria in South Africa.** *Kidney Int* 2006, **69**(12):2243 2250.
23. Navaneethan SD, Aloudat S, Singh S: **A systematic review of patient and health system characteristics associated with late referral in chronic kidney disease.** *BMC Nephrol* 2008, **9**:3.
24. Sarafidis PA, Li S, Chen SC, Collins AJ, Brown WW, Klag MJ, Bakris GL: **Hypertension awareness, treatment, and control in chronic kidney disease.** *Am J Med* 2008, **121**(4):332 340.
25. Peer N, Steyn K, Dennison CR, Levitt NS, Nyo MT, Nel JH, Commerford PJ, Fourie JM, Hill MN: **Determinants of target organ damage in black hypertensive patients attending primary health care services in Cape Town: the Hi Hi study.** *Am J Hypertens* 2008, **21**(8):896 902.
26. Gold CH, Isaacson C, Levin J: **The pathological basis of end stage renal disease in blacks.** *S Afr Med J* 1982, **61**(8):263 265.
27. Seedat YK, Naicker S, Rawat R, Parsoo I: **Racial differences in the causes of end stage renal failure in Natal.** *S Afr Med J* 1984, **65**(24):956 958.
28. Veriava Y, du Toit E, Lawley CG, Milne FJ, Reinach SG: **Hypertension as a cause of end stage renal failure in South Africa.** *J Hum Hypertens* 1990, **4**(4):379 383.
29. Arogundade FA, Barsoum RS: **CKD prevention in Sub Saharan Africa: a call for governmental, nongovernmental, and community support.** *Am J Kidney Dis* 2008, **51**(3):515 523.
30. Lucas GM, Lau B, Atta MG, Fine DM, Keruly J, Moore RD: **Chronic kidney disease incidence, and progression to end stage renal disease, in HIV infected individuals: a tale of two races.** *J Infect Dis* 2008, **197**(11):1548 1557.
31. Alebiosu CO, Ayodele OE: **The increasing prevalence of diabetic nephropathy as a cause of end stage renal disease in Nigeria.** *Trop Dr* 2006, **36**:218 219.
32. Karaye KM, Habib AG: **Dyslipidaemia in patients with established cardiovascular disease in Sub Saharan Africa: a systematic review and meta analysis.** *Eur J Prev Cardiol* 2012, Epub 2012 September 5. Pubmed PMID: 22952291.
33. Harper CR, Jacobson TA: **Managing dyslipidemia in chronic kidney disease.** *J Am Coll Cardiol* 2008, **51**(25):2375 2384.
34. Murthy K, Stevens LA, Stark PC, Levey AS: **Variation in the serum creatinine assay calibration: a practical application to glomerular filtration rate estimation.** *Kidney Int* 2005, **68**(4):1884 1887.
35. Eppenga W, van Luin M, Richter C, Derijks H, De Smet P, Wensing M: **The validity of the modification of diet in renal disease formula in HIV infected patients: a systematic review.** *J Nephrol* 2014, **27**(1):11 18.

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CHAPTER 3

ASSOCIATION OF KIDNEY FUNCTION AND WAIST CIRCUMFERENCE WITH URIC ACID LEVELS IN SOUTH AFRICANS

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ORIGINAL ARTICLE

Association of Kidney Function and Waist Circumference with Uric Acid Levels in South Africans

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Abstract

Background: Recent evidence that hyperuricemia is associated with incident chronic kidney disease (CKD) provides a potential therapeutic target for CKD that has not been explored in Africans. With hyperuricemia and gout increasing globally, we sought to determine their prevalence in South Africans with varying kidney function levels.

Methods: This was a cross-sectional study of ambulatory adult patients presenting at a General Internal Medicine Outpatients Clinic between September 2012 and March 2014. Demographic, clinical, and laboratory data collected were analyzed using STATA11. Odds ratios (ORs) and 95% confidence intervals were determined using multivariable logistic regression with bootstrapping.

Results: There were 225/261 (86.2%) black/Africans, 31/261 (11.9%) Indian South Africans, 3/261 (1.1%) Caucasians, and 2/261 (<1%) mixed ancestry South Africans. Mean age was 51.3 ± 14.5 years. Median (interquartile range) estimated glomerular filtration rate (eGFR) was 71 (38) mL/min/1.73 m^2 and 39.8% (104/261) of patients had CKD. Hyperuricemia prevalence was 43.7% (114/261) and increased from 16.7% in patients with eGFR ≥90 mL/min/1.73 m^2 to 74.2% with eGFR <30 mL/min/1.73 m^2 ($P < 0.001$). Gout prevalence was 5.4% (14/261), with equal distribution across eGFR categories (0.814). Factors independently associated with hyperuricemia were eGFR <90 [ORs 3.24 (1.15–9.14), 7.28 (2.26–23.49), and 7.88 (1.95–31.82) for eGFR 60–89.9, 30–60, and <30, respectively], albuminuria [2.32 (1.11–4.85)], and waist circumference [1.04 (1.01–1.06) per 1 cm increase]. In univariate and multivariable analysis, gout was positively associated with male gender and cardiovascular disease, while it was negatively associated with African ancestry, but none of these factors remained significant after bootstrapping; ORs 6.65 (0.64–69.24), 4.14 (0.61–28.07), and 0.18 (0.01–2.21), respectively.

Conclusion: Hyperuricemia prevalence was high, with CKD and waist circumference being the strongest predictors. Gout was uncommon in black Africans. With population data lacking, screening high-risk individuals may provide insight into the burden of hyperuricemia and gout in South Africa.

Keywords: cardiovascular, chronic kidney disease, gout, hyperuricemia, South African, waist circumference

Background

Recent population studies have reported a significant increase in the prevalence of hyperuricemia and gout worldwide.[1–6] This has been in parallel with a rising prevalence of obesity with other components of the metabolic syndrome such as diabetes and hypertension.[7] Other contributing factors include medications that increase serum uric acid levels, such as diuretics, low-dose aspirin, alcohol, sugar-sweetened soft drinks, and other fructose consumption. Hyperuricemia is associated with chronic kidney disease (CKD) and occurs in >50% of patients by the time of dialysis initiation.[8] Historically, this association between hyperuricemia and CKD was not considered significant, but there has been renewed interest following evidence that hyperuricemia is associated with the development of CKD.[8]

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Earlier observational and population studies showed that higher serum uric acid levels, even in the normal range, were associated with impaired renal function.[6,9,10] Subsequent longitudinal data have suggested that hyperuricemia may be a risk factor for incident CKD in individuals with normal kidney function and disease progression in established CKD.[8,11,12] Furthermore, urate-lowering treatment may retard CKD progression.[13] Thus, hyperuricemia provides a potential therapeutic target for primary and secondary prevention of CKD, which has not been evaluated in South Africa. Prevalence of hyperuricemia and gout is unknown in the South African population as well as in high-risk individuals. In two studies of healthy South African volunteers, African subjects were found to have significantly lower serum uric acid levels despite higher blood pressure levels compared with Caucasian subjects; however, gout was not evaluated.[14, 15] The aim of this study was to evaluate hyperuricemia prevalence as well as associated factors in ambulatory South African patients.

Subjects and Methods

Data were collected for this cross-sectional study between September 2012 and March 2014 at the General Internal Medicine Outpatients' Clinic at King Edward VIII Hospital, an 800-bed public-sector hospital in Durban, South Africa. The hospital predominantly serves black African patients, reflecting the population demographics in our province that consists of 86.9% black Africans, 7.5% Indian South African, 4% white South Africans, and 1.3% colored/mixed ancestry South Africans.[16] The clinic provides care to adults with various chronic diseases, predominantly hypertension, diabetes, cardiovascular disease, respiratory diseases, and human immunodeficiency virus (HIV). Clinic attendees were invited to undergo screening for CKD, related risk factors, and complications. Inclusion criteria were stable ambulatory patients aged ≥18 years. We excluded patients with an intercurrent illness, for example, infection, malignancy, dialysis patients, and patients requiring in-hospital care. All participants were enrolled following written informed consent. Ethical approval was granted by the University of KwaZulu-Natal Biomedical Research Ethics Committee (Protocol number: BE179/11).

Data collection

Data were collected during clinic consultations by the principal investigator and research nurse. We documented the following: (1) History: age, gender, lifestyle factors, prevalent comorbid diseases, for example, hypertension, diabetes, cardiovascular disease (carotid atherosclerosis, cerebrovascular, coronary artery and peripheral vascular disease), HIV, and gout, and current medication; (2) Physical examination: including blood pressure, weight, height, and waist circumference; (3) Investigations: blood samples obtained for serum creatinine, urea, electrolytes, uric acid, glucose, total cholesterol, serum triglycerides, and urine specimens for urine albumin:creatinine ratio were analyzed at the King Edward VIII Hospital Laboratory, which is part of the state-funded National Health Laboratory Services (NHLS) network in South Africa.

Definitions

We defined CKD as the presence, for ≥3 months, of estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or albuminuria and/or abnormal kidney ultrasonography. We used the Modification of Diet in Renal Disease (MDRD) eGFR formula.[17] We omitted the African American correction factor, as that was shown to improve MDRD-eGFR accuracy in South Africans.[18] Prevalent comorbid disease was based on self-reported prior diagnosis with current medication and clinical records used for verification in all patients. Patients with elevated nonfasting total cholesterol underwent repeated blood sampling following an overnight fast and were classified as dyslipidemic if total cholesterol remained >5 mmol/L and/or serum triglycerides >1.5 mmol/L. Hyperuricemia was defined by serum uric acid level >0.36 mmol/L in females and >0.42 mmol/L in males. Gout patients were all receiving allopurinol.

Statistical analysis

Data were analyzed using Intercooled Stata version 11 (TX). Continuous data are expressed as mean ± standard deviation and categorical data as proportions. Between-group differences were evaluated using one-way analysis of variance and chi-square test, respectively. Fisher's exact test was used where applicable. Non-normal data were summarized using median (interquartile range) and the Kruskal Wallis test used for between-group comparisons. Multivariable logistic regression analysis was performed to assess factors associated with hyperuricemia and gout, with results expressed as odds ratio with 95% confidence interval [OR (95% CI)]. To further improve the accuracy of the observed associations, models were bootstrapped using 5000 resamples.

Results

In total, 283 patients met the inclusion criteria; 22 (7.8%) were excluded for unavailable serum uric acid levels. Thus, 261 (92.2%) patients were analyzed and 161 (61.7%) were females. Patients of African ancestry accounted for 86.2% (225/261), in keeping with the provincial population profile. The remaining 13.7% (36/261) patients comprised 31 Indian South Africans, 3 Caucasian South Africans, and 2 colored/mixed ancestry South Africans. Males had higher alcohol consumption, serum uric acid, and serum creatinine levels, as well as higher proportions with gout and albuminuria; females had significantly more obesity (Table 1). Hyperuricemia was found in 114/261 (43.7%) patients and gout in 14/261 (5.4%). Nine of the 14 patients with gout were African, while the other 5/14 patients consisted of Indian (3), white (1), and 1 mixed ancestry patient; thus, gout frequency in Africans was 4% (9/225). The prevalence of hyperuricemia and hypertension increased significantly with worsening renal function, while prevalence of diabetes, HIV, as well as gout remained unchanged as they did not increase significantly as renal function declined (Fig. 1). Of those with hyperuricemia, 49 (43%) had normal renal function (MDRD-eGFR ≥60 mL/min/1.73 m^2). Table 2 shows patient characteristics by MDRD-eGFR. Age, systolic blood pressure, furosemide use, and serum uric acid increased significantly with declining eGFR ($P < 0.001$). Hyperuricemic patients were older, more likely to have history of hypertension, higher

TABLE 1. DEMOGRAPHIC, CLINICAL, AND LABORATORY CHARACTERISTICS OF PATIENTS STUDIED

Parameters	*Total,* n = *261*	*Males,* n = *100*	*Females,* n = *161*	P
Demographics				
Age (years)	51.3 ± 14.5	51.5 ± 15.4	51.1 ± 14.0	0.871
African, *n* (%)	225 (86.2)	86 (86)	139 (86.3)	0.939
Lifestyle habits				
Smoking, *n* (%)	13 (5)	7 (7)	6 (3.7)	0.237
Alcohol use, *n* (%)	33 (12.6)	27 (27)	6 (3.7)	<0.001
Clinical and laboratory parameters				
Hypertension, *n* (%)	191 (73.2)	73 (73)	118 (73.3)	0.959
Diabetes, *n* (%)	72 (27.6)	30 (30)	42 (26.1)	0.492
HIV, *n* (%)	47 (18)	14 (14)	33 (20.5)	0.184
Cardiovascular disease, *n* (%)	73 (28)	34 (34)	39 (24.2)	0.087
Dyslipidemia, *n* (%)	78 (29.9)	36 (36)	42 (26.1)	0.089
Gout, *n* (%)	14 (5.4)	11 (11)	3 (1.9)	0.001
Hyperuricemia, *n* (%)	114 (43.7)	49 (49)	65 (40.4)	0.172
Diuretic use, *n* (%)	170 (65.1)	61 (61)	109 (67.7)	0.269
ACE inhibitor use, *n* (%)	142 (54.4)	59 (59)	83 (51.6)	0.240
ARB use, *n* (%)	7 (2.7)	0	7 (4.4)	0.035
Waist circumference (cm)	100.2 ± 14.7	97.2 ± 13.6	102.1 ± 15.2	0.011
Body mass index (kg/m^2)	30.9 ± 7.3	27.9 ± 6.5	32.7 ± 7.1	<0.001
Systolic blood pressure (mmHg)	127.3 ± 21.5	127.8 ± 21.3	127.0 ± 21.7	0.784
Diastolic blood pressure (mmHg)	73.6 ± 15.4	76.4 ± 14.1	71.9 ± 16.0	0.022
Total cholesterol (mM)	4.5 ± 1.2	4.48 ± 1.4	4.6 ± 1.1	0.450
Serum triglycerides (mM)[a]	1.32 (0.89 2.06)	1.47 (0.93 2.28)	1.24 (0.88 1.90)	0.118
Uric acid (mM)	0.38 ± 0.12	0.43 ± 0.13	0.35 ± 0.11	<0.001
Serum creatinine (μM)[a]	84 (68 110)	98 (81 131.5)	76 (62 98)	<0.001
MDRD-eGFR (mL/min/1.73 m^2)[a]	71 (51 89)	71 (51 91.5)	70 (51 88)	0.993
MDRD-eGFR <60, *n* (%)	98 (37.6)	35 (35)	63 (39.1)	0.503
Albuminuria, *n* (%)	118 (45.2)	56 (56)	62 (38.5)	0.006
CKD, *n* (%)	104 (39.8)	38 (38)	66 (41)	0.631

[a]Non normal data are expressed as median (25th 75th percentile values).
ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

systolic and diastolic blood pressure, obesity, and worse renal function compared with normouricemic patients (Table 3).

Results of the univariate and multivariable logistic regression analysis for the odds of hyperuricemia are shown in Table 4. Variables included in the models were as follows: MDRD-eGFR, albuminuria, hypertension, aspirin use, angiotensin-converting enzyme inhibitor and diuretic use, waist circumference, dyslipidemia, age, alcohol consumption, as well as gender. Factors independently associated with hyperuricemia were as follows: MDRD-eGFR, albuminuria, and waist circumference, all of which remained robust in subsequent bootstrap resampling. Furthermore, the association with MDRD-eGFR occurred even at higher eGFR levels (60 89.9 mL/min/1.73 m^2). The association with age and aspirin, angiotensin-converting enzyme inhibitor, and diuretic use and dyslipidemia observed in univariate analysis was eliminated in the multivariable logistic regression models. No association was seen with alcohol consumption, gender, ethnicity, or diabetes.

Multivariable logistic regression analysis of determinants for gout (without bootstrapping) showed positive independent association with male gender [OR 6.65 (1.68 26.29), $P = 0.007$] and cardiovascular disease [OR 4.14 (1.21 14.18), $P = 0.024$], while African ancestry decreased the odds of gout [OR 0.18 (0.05 0.66), $P = 0.01$]; adjusted for gender, ethnicity, cardiovascular disease, dyslipidemia, and MDRD-eGFR. However, all associations earlier noted with gout were eliminated in the bootstrapped models; bootstrap-adjusted OR for male gender [6.65 (0.64 69.24), $P = 0.113$], African ancestry [0.18 (0.01 2.21), $P = 179$], cardiovascular disease [4.14 (0.61 28.07), $P = 0.146$], dyslipidemia [2.22 (0.30 16.29), $P = 0.431$], and MDRD-eGFR [1.46 (0.39 5.45), $P = 0.570$].

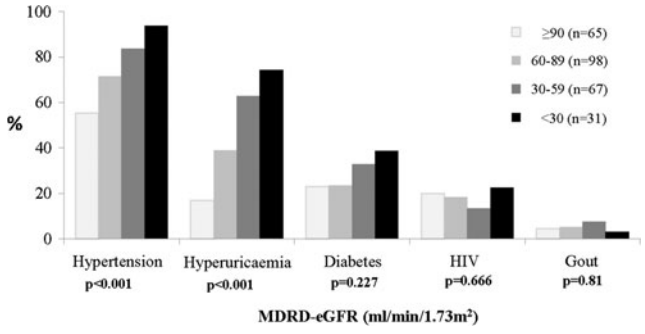

FIG. 1. Prevalence of hyperuricemia, gout, and comorbid diseases according to estimated glomerular filtration rate category. eGFR, estimated glomerular filtration rate; HIV, human immunodeficiency virus; MDRD, Modification of Diet in Renal Disease. eGFR, estimated glomerular filtration rate.

Discussion

We observed a high prevalence of hyperuricemia (43.7%) in this cohort characterized by a high cardiometabolic risk profile, with hypertension in >70% and variable kidney

Table 2. Demographic, Clinical, and Laboratory Characteristics by Glomerular Filtration Rate Category

Parameters	*eGFR ≥90,* n = *65*	*eGFR 60 89.9,* n = *98*	*eGFR 30 59.9,* n = *67*	*eGFR <30,* n = *31*	P
Age (years)	42.5 ± 12.8	51.8 ± 14.2	56.4 ± 13.2	56.8 ± 13.8	<0.001
Male, *n* (%)	27 (41.5)	38 (38.8)	19 (28.4)	16 (51.6)	0.143
African, *n* (%)	56 (86.2)	81 (82.7)	61 (91.0)	27 (87.1)	0.497
Alcohol use, *n* (%)	12 (18.5)	9 (9.2)	6 (9)	6 (19.4)	0.162
Cardiovascular disease, *n* (%)	13 (20.0)	29 (29.6)	22 (32.8)	9 (29.0)	0.394
Dyslipidemia, *n* (%)	18 (27.7)	25 (25.5)	19 (28.4)	16 (51.6)	0.044
Diuretic use, *n* (%)	31 (47.7)	65 (66.3)	50 (74.6)	24 (77.4)	0.004
Hydrochlorothiazide, *n* (%)	18 (27.7)	29 (29.6)	21 (31.3)	3 (9.7)	0.128
Furosemide, *n* (%)	13 (20.0)	37 (37.8)	29 (43.3)	22 (71.0)	<0.001
Spironolactone, *n* (%)	1 (1.5)	7 (7.1)	8 (11.9)	2 (6.5)	0.134
ACE inhibitor use, *n* (%)	27 (41.5)	57 (58.2)	39 (58.2)	19 (61.3)	0.118
ARB use, *n* (%)	1 (1.5)	30 (3.1)	3 (4.5)	0	0.56
Waist circumference (cm)	97.8 ± 16.1	101.3 ± 13.6	102.9 ± 15.9	95.8 ± 11.1	0.069
Body mass index (kg/m^2)	29.9 ± 7.6	31.0 ± 6.9	32.6 ± 8.0	28.6 ± 5.21	0.048
Systolic blood pressure (mmHg)	118.8 ± 19.3	125.1 ± 19.0	133.1 ± 23.1	139.7 ± 21.6	<0.001
Diastolic blood pressure (mmHg)	70.2 ± 13.3	73.9 ± 15.4	75.9 ± 17.4	74.7 ± 14.6	0.175
Total cholesterol (mM)	4.5 ± 1.3	4.6 ± 1.3	4.7 ± 1.2	4.4 ± 1.0	0.733
Serum triglycerides (mM)[a]	1.36 (0.84 2.27)	1.17 (0.84 1.85)	1.37 (1.05 2.09)	1.55 (1.03 2.26)	0.34
Uric acid (mM)	0.32 ± 0.10	0.37 ± 0.12	0.41 ± 0.12	0.45 ± 0.13	<0.001
Serum creatinine (μM)[a]	59 (54 72)	78 (70 90)	109 (94 127)	281 (212 631)	<0.001
MDRD-eGFR (mL/min/1.73 m^2)[a]	103 (96 115)	75 (69 81)	51 (43 55)	19 (8 25)	<0.001
Albuminuria, *n* (%)	23 (35.4)	33 (33.7)	32 (47.8)	30 (96.8)	<0.001

[a]Non normal data are expressed as median (25th 75th percentile values).

function. Our data provide insight into the burden of hyperuricemia that is lacking in South Africans. This finding is comparable to prevalence estimates in high-risk subjects studied elsewhere. Some of the earliest studies reported hyperuricemia in 25% 40% of hypertensive patients.[19] A recent study of Taiwanese hypertensive patients found hyperuricemia in 43% of females and 35% of males.[20] One of the few published studies in sub-Saharan Africa reported hyperuricemia in 25% of type II diabetes patients in Nigeria.[21] Hyperuricemia prevalence in our study increased with worsening kidney function; 74.2% of patients with eGFR <30 mL/min/1.73 m^2 compared with 16.7% in those with eGFR ≥90 mL/min/1.73 m^2. This is similar to the prevalence of 79.1% and 72.3% with eGFR <30 mL/min/1.73 m^2 reported in the United States and China, respectively, versus 11.2% in those with eGFR ≥90 mL/min/1.73 m^2 in the United States and 29.3% in Chinese participants with eGFR ≥60 mL/min/1.73 m^2.[6,22,23] Apart from CKD, hyperuricemia is also associated with obesity and other components of the metabolic syndrome.[7] This was also evident in our study, as odds of hyperuricemia increased by 3% (95% CI 1% 6%) for every cm increase in waist circumference, but not with BMI, emphasizing the greater association with central obesity observed by others.[21]

The other major finding in this study was that of prevalent hyperuricemia even with normal kidney function, with the odds of hyperuricemia threefold greater in those with MDRD-eGFR 60 89.9 mL/min/1.73 m^2, after adjusting for other risk factors. This raises the possible presence of other determinants of serum uric acid such as high dietary intake of protein, purines, and/or fructose, however, we did not evaluate these. Hyperuricemia prevalence in high-risk patients is much higher than in the general population, based on evidence from recent large studies.[1,2,5,24–27] This could explain the rising global prevalence of gout[1–6] since hyperuricemia is a major risk factor for gout. There are no population data on gout in South Africa. Hospital-based studies in the 1990s suggested that gout was more common in Africans than previously thought.[28,29] Gout prevalence in the present study (5.4%) was higher than the population prevalence of 4.3% in the United States, 2.5% in the United Kingdom, 0.9% in Italy, and 2.1% in Taiwan.[4–6,24] While this probably reflects the high-risk profile of our cohort, it is much lower than in high-risk individuals in other studies and remained low across CKD stages. In the U.S. studies cited above, gout prevalence increased with declining GFR and reached 33% at eGFR <30 mL/min/1.73 m^2.[6,22] The lower prevalence in our study could reflect under-recognition. Another potential explanation may be lower gout frequency in Africans compared with other ethnic groups. The initial observation of lower odds of gout with African ancestry in the present study did not reach statistical significance in the 5000 bootstrap resamples. Nonetheless, the potential protective effect against gout in Africans warrants further investigation, in view of the lower uric acid levels found in black South Africans in the studies cited earlier.[14,15] However, we did not find an association between hyperuricemia and ethnicity in our study.

Strengths and limitations

The strength of this study is the heterogeneous study population from a general internal medicine clinic rather than a specialized endocrinology or nephrology clinic. This is unique in presenting a wide spectrum of cardiometabolic risk markers in the same cohort, such as central obesity, hypertension, diabetes, and CKD. In the absence of population studies in South Africa, our contribution is valuable because hyperuricemia has not been studied to a significant degree

Table 3. Differences Between Hyperuricemic and Normouricemic Patients

Parameters	*Hyperuricemic,* n = *114*	*Normouricemic,* n = *147*	P
Age (years)	54.4 ± 13.0	48.8 ± 15.2	0.002
Male, *n* (%)	49 (43)	51 (34.7)	0.172
African, *n* (%)	98 (86)	127 (86.4)	0.920
Lifestyle habits			
Smoking, *n* (%)	2 (1.8)	11 (7.5)	0.035
Alcohol use, *n* (%)	13 (11.4)	20 (13.6)	0.595
Clinical and laboratory parameters			
Hypertension, *n* (%)	100 (87.7)	91 (61.9)	<0.001
Diabetes, *n* (%)	37 (32.5)	35 (23.8)	0.121
HIV, *n* (%)	14 (12.3)	33 (22.5)	0.034
Cardiovascular disease, *n* (%)	39 (34.2)	34 (23.1)	0.048
Dyslipidemia, *n* (%)	45 (39.5)	33 (22.5)	0.003
Gout, *n* (%)	8 (7)	6 (4.1)	0.296
Diuretic use, *n* (%)	85 (74.6)	85 (57.8)	0.005
Hydrochlorothiazide, *n* (%)	26 (22.8)	45 (30.6)	0.160
Furosemide, *n* (%)	60 (52.6)	41 (27.9)	<0.001
Spironolactone, *n* (%)	11 (9.7)	7 (4.8)	0.122
ACE inhibitor use, *n* (%)	73 (64)	69 (46.9)	0.006
ARB use, *n* (%)	5 (4.4)	2 (1.4)	0.133
Waist circumference (cm)	103.4 ± 15.0	97.7 ± 14.1	0.002
Body mass index (kg/m^2)	31.9 ± 7.2	30.0 ± 7.2	0.037
Systolic blood pressure (mmHg)	133.8 ± 21.9	122.3 ± 19.9	<0.001
Diastolic blood pressure (mmHg)	76.8 ± 16.7	71.1 ± 14.0	0.003
Glucose (mM)[a]	5.7 (4.8 6.8)	5.2 (4.8 6.2)	0.04
Total cholesterol (mM)	4.6 ± 1.2	4.5 ± 1.2	0.565
Serum triglycerides (mM)[a]	1.50 (1.04 2.16)	1.19 (0.77 1.89)	0.004
Uric acid (mM)	0.49 ± 0.1	0.30 ± 0.1	<0.001
Serum creatinine (μM)[a]	100 (83 145)	75 (61 93)	<0.001
MDRD-eGFR (mL/min/1.73 m^2)[a]	56.5 (36 74)	80.4 (64 100)	<0.001
MDRD-eGFR <60, *n* (%)	65 (57)	33 (22.5)	<0.001
Albuminuria			
Microalbuminuria, *n* (%)	29 (25.4)	34 (23.1)	0.665
Macroalbuminuria, *n* (%)	38 (33.3)	18 (12.2)	<0.001
CKD, *n* (%)	67 (58.8)	37 (25.2)	<0.001

[a]Non normal data are expressed as median (25th 75th percentile values).
HIV, human immunodeficiency virus.

Table 4. Univariate and Multivariable Logistic Regression Analysis of Factors Associated with Hyperuricemia

Parameters	*Unadjusted OR (95% CI)*	P	*Adjusted OR*[c] *(95% CI)*	P	*Adjusted OR*[d] *(95% CI)*	P
MDRD-eGFR[a]						
60 89.9	3.11 (1.45 6.68)	0.004	3.24 (1.36 7.72)	0.008	3.24 (1.15 9.14)	0.026
30 60	8.24 (3.65 18.65)	<0.001	7.28 (2.83 18.77)	<0.001	7.28 (2.26 23.49)	0.001
<30	14.11 (5.02 39.66)	<0.001	7.88 (2.42 25.63)	0.001	7.88 (1.95 31.82)	0.004
Albuminuria	2.68 (1.62 4.44)	<0.001	2.32 (1.22 4.39)	0.010	2.32 (1.11 4.85)	0.026
Hypertension	4.40 (2.30 8.43)	<0.001	2.63 (0.99 6.98)	0.051	2.63 (0.86 8.05)	0.089
Low-dose aspirin	2.58 (1.53 4.35)	<0.001	1.45 (0.74 2.87)	0.281	1.45 (0.69 3.07)	0.328
ACE inhibitor	2.01 (1.22 3.32)	0.006	1.20 (0.62 2.33)	0.587	1.20 (0.58 2.48)	0.619
Diuretic	2.14 (1.25 3.65)	0.005	0.84 (0.39 1.81)	0.656	0.84 (0.35 2.00)	0.693
Waist circumference	1.03 (1.01 1.05)	0.003	1.03 (1.01 1.06)	0.002	1.04 (1.01 1.06)	0.009
Dyslipidemia	2.06 (1.15 3.69)	0.015	1.38 (0.69 2.79)	0.364	1.38 (0.63 3.12)	0.433
Age group[b]	1.78 (1.29 2.45)	<0.001	0.95 (0.62 1.46)	0.802	0.83 (0.48 1.42)	0.492
Male gender	1.41 (0.85 2.35)	0.173	1.66 (0.84 3.25)	0.143	1.66 (0.71 3.84)	0.240
African ancestry	0.96 (0.48 1.96)	0.920	0.70 (0.30 1.62)	0.403	0.70 (0.27 1.80)	0.458
Alcohol	0.82 (0.39 1.72)	0.596	0.87 (0.33 2.33)	0.787	0.87 (0.25 3.06)	0.833

[a]MDRD eGFR ≥90.
[b]age <40 years.
[c]adjusted model before bootstrapping.
[d]estimated from 5000 bootstrap samples.
OR, odds ratio.

in South Africans, while published studies of gout largely evaluated rheumatology clinic patients. Furthermore, all patients were seen by one team comprising the principal investigator and research nurse thus minimizing observer bias. The major study limitation is its cross-sectional design as causal relationships cannot be evaluated. Selection bias is inevitable in such a hospital-based study, and thus, results cannot be generalized to the South African population. Nonetheless, screening high-risk individuals may be a cost-effective strategy in the initial epidemiological studies in resource-limited settings. A further major limitation is the small size of our sample, which is evident in the wide confidence intervals for both hyperuricemia and, even more so, for gout. The small number of patients of non-African descent (13% of the population) may be another limitation that could explain the lack of association between hyperuricemia and gout with ethnicity. The small number of those with gout could also account for the lack of an increase in gout prevalence with worsening CKD in this study.

Conclusion

Hyperuricemia prevalence was high and significantly associated with CKD as well as waist circumference in this cohort, independent of other factors. This may suggest a rising background population prevalence for hyperuricemia as observed elsewhere. Unlike in other studies, gout prevalence was lower in our study, irrespective of eGFR level, with suggestion of a negative association observed with African ancestry, and thus, further investigation is required. Where population data are lacking, as in South Africa, screening of high-risk patients may provide valuable data on the burden of hyperuricemia and gout to guide future research into the potential role of uric acid and the need for urate-lowering strategies.

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Authors' Contributions

N.D.M. was responsible for the conception and design of the study, data collection, and interpretation and writing the initial draft manuscript; T.D. contributed to the data collection and revision of the manuscript; A.G.H.A. provided intellectual input to the study protocol and draft manuscript; S.N. provided intellectual input to the study protocol and revision of the manuscript. All the authors approved the final version.

Author Disclosure Statement

No conflicting financial interests exist.

References

1. Zhu Y, Pandya BJ, Choi HK. Prevalence of gout and hyperuricemia in the US general population: The National Health and Nutrition Examination Survey 2007 2008. *Arthritis Rheum* 2011;63:3136 3141.
2. Liu B, Wang T, Zhao HN, et al. The prevalence of hyperuricemia in China: A meta analysis. *BMC Public Health* 2011;11:832.
3. Robinson PC, Taylor WJ, Merriman TR. Systematic review of the prevalence of gout and hyperuricaemia in Australia. *Intern Med J* 2012;42:997 1007.
4. Kuo CF, Grainge MJ, Mallen C, et al. Rising burden of gout in the UK but continuing suboptimal management: A nationwide population study. *Ann Rheum Dis* 2015;74:661 667.
5. Trifiro G, Morabito P, Cavagna L, et al. Epidemiology of gout and hyperuricaemia in Italy during the years 2005 2009: A nationwide population based study. *Ann Rheum Dis* 2013;72:694 700.
6. Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009 10. *PLoS One* 2012;7:e50046.
7. Rho YH, Zhu Y, Choi HK. The epidemiology of uric acid and fructose. *Semin Nephrol* 2011;31:410 419.
8. Johnson RJ, Nakagawa T, Jalal D, et al. Uric acid and chronic kidney disease: Which is chasing which? *Nephrol Dial Transplant* 2013;28:2221 2228.
9. Rosolowsky ET, Ficociello LH, Maselli NJ, et al. High normal serum uric acid is associated with impaired glomerular filtration rate in nonproteinuric patients with type 1 diabetes. *Clin J Am Soc Nephrol* 2008;3:706 713.
10. Chen N, Wang W, Huang Y, et al. Community based study on CKD subjects and the associated risk factors. *Nephrol Dial Transplant* 2009;24:2117 2123.
11. Yamada T, Fukatsu M, Suzuki S, et al. Elevated serum uric acid predicts chronic kidney disease. *Am J Med Sci* 2011; 342:461 466.
12. Li L, Yang C, Zhao Y, et al. Is hyperuricemia an independent risk factor for new onset chronic kidney disease? A systematic review and meta analysis based on observational cohort studies. *BMC Nephrol* 2014;15:122.
13. Bose B, Badve SV, Hiremath SS, et al. Effects of uric acid lowering therapy on renal outcomes: A systematic review and meta analysis. *Nephrol Dial Transplant* 2014; 29:406 413.
14. Palmer IM, Schutte AE, Huisman HW, et al. A comparison of uric acid levels in Black African vs Caucasian women from South Africa: The POWIRS study. *Ethn Dis* 2007;17: 676 681.
15. Palmer IM, Schutte AE, Huisman HW. Uric acid and the cardiovascular profile of African and Caucasian men. *J Hum Hypertens* 2010;24:639 645.
16. Statistics South Africa. Census 2011 Municipal report, KwaZulu Natal. Report No. 03 01 53. http://beta2.statssa.gov.za/census/census 2011/census products/KZN Municipal Report.pdf accessed May 6, 2013.
17. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation for the Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461 470.
18. Madala ND, Nkwanyana N, Dubula T, et al. Predictive performance of eGFR equations in South Africans of African and Indian ancestry compared with (99 m)Tc DTPA imaging. *Int Urol Nephrol* 2012;44:847 855.
19. Cannon PJ, Stason WB, Demartini FE, et al. Hyperuricemia in primary and renal hypertension. *N Engl J Med* 1966;275: 457 464.
20. Lin C S, Lee W L, Hung Y J, et al. Prevalence of hyperuricemia and its association with antihypertensive treatment in hypertensive patients in Taiwan. *Int J Cardiol* 2012; 156:41 46.

21. Ogbera AO, Azenabor AO. Hyperuricaemia and the meta bolic syndrome in type 2 DM. *Diabetol Metab Syndr* 2010; 2:24.
22. Juraschek SP, Kovell LC, Miller ER, 3rd, et al. Association of kidney disease with prevalent gout in the United States in 1988 1994 and 2007 2010. *Semin Arthritis Rheum* 2013; 42:551 561.
23. Li Z, Liu Q, Mao H, et al. Gender difference in the as sociation of hyperuricemia with chronic kidney disease in Southern China. *Kidney Blood Press Res* 2012;36:98 106.
24. Kuo CF, See LC, Luo SF, et al. Gout: An independent risk factor for all cause and cardiovascular mortality. *Rheuma tology* 2010;49:141 146.
25. Lohsoonthorn V, Dhanamun B, Williams MA. Prevalence of hyperuricemia and its relationship with metabolic syn drome in Thai adults receiving annual health exams. *Arch Med Res* 2006;37:883 889.
26. Chuang SY, Lee SC, Hsieh YT, et al. Trends in hyperuri cemia and gout prevalence: Nutrition and Health Survey in Taiwan from 1993 1996 to 2005 2008. *Asia Pac J Clin Nutr* 2011;20:301 308.
27. Conen D, Wietlisbach V, Bovet P, et al. Prevalence of hyperuricemia and relation of serum uric acid with car diovascular risk factors in a developing country. *BMC Public Health* 2004;4:9.
28. Cassim B, Mody GM, Deenadayalu VK, et al. Gout in black South Africans: A clinical and genetic study. *Ann Rheum Dis* 1994;53:759 762.
29. Tikly M, Bellingan A, Lincoln D, et al. Risk factors for gout: A hospital based study in urban black South Africans. *Rev Rheum Engl Ed* 1998;65:225 231.

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CHAPTER 4

PREVALENCE AND EARLIER OCCURRENCE OF CHRONIC KIDNEY DISEASE-RELATED METABOLIC ABNORMALITIES IN SOUTH AFRICANS

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PREVALENCE AND EARLIER OCCURRENCE OF CHRONIC KIDNEY DISEASE-RELATED METABOLIC ABNORMALITIES IN SOUTH AFRICANS

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Abstract

Background

People of African descent in developed countries have been reported to have a high prevalence and earlier onset of chronic kidney disease (CKD) metabolic complications. Data are lacking in sub-Saharan Africa, with many patients with CKD complications unlikely to access specialized nephrology care due to the limited number of nephrologists. We sought to determine the prevalence and stage of occurrence of metabolic abnormalities in a cohort of South Africans.

Methods

We studied 283 stable ambulatory patients attending a General Internal Medicine clinic from September 2012 to March 2014, following informed consent. Data collected were analysed with Stata11. Logistic regression analysis was used to assess factors associated with various metabolic abnormalities and results expressed as odds ratios with 95% confidence interval.

Results

There were 117 females (62.5%) and 244 (86.2%) patients were black/African. Mean age was 51.3 ± 14.5 years, median estimated glomerular filtration rate (eGFR) (25^{th}-75^{th} percentile) was 71 (51-89) ml/min/1.73m^2 and 43.8% had CKD. As eGFR declined from eGFR ≥90 ml/min/1.73m^2 to eGFR <30 ml/min/1.73m^2, metabolic acidosis increased from 11.6% to 72.7%, anaemia prevalence increased from 2.9% to 69.7% and hyperphosphataemia from 10.1% to 48.5% ($p<0.001$, respectively), while hypocalcaemia increased from 1.5% to 18.2% ($p=0.003$). Worsening CKD stage was the most significant factor associated with each abnormality. In addition, metabolic acidosis showed significant positive association with macroalbuminuria [5.05 (2.02-12.6), $p\leq0.001$] and negative association with diuretic use (0.21 (0.08-0.54, $p<0.01$),

independent of eGFR, while an independent negative relationship was also observed between diuretic use and hypocalcaemia [0.14 (0.03-0.59), p<0.01].

Conclusion

Severe metabolic abnormalities were prevalent across the GFR spectrum in this cohort of African patients, with some present at earlier stages of CKD. Greater efforts are needed for early screening and treatment of CKD-related abnormalities, especially in resource-limited settings since treatment of these disorders may retard CKD progression.

Keywords: Acidosis, African, anaemia, chronic kidney disease, glomerular filtration rate, hyperphosphataemia, hypocalcaemia

Background

The Kidney Disease Improving Global Outcomes (KDIGO) guidelines for the management of chronic kidney disease (CKD) provide specific evidence-based recommendations for managing various metabolic and endocrine complications associated with CKD such as anaemia, mineral metabolism disturbances as well as metabolic acidosis (1). These disorders are associated with a higher risk of CKD progression in pre-dialysis patients with poor renal outcomes (2-8). While there is conclusive evidence that anaemia correction improved outcomes (3), data on mineral metabolism disorders are less conclusive although observational studies have reported improved outcomes with various interventions (9). Correction of metabolic acidosis has also been shown to preserve renal function (10-12). In the South African public healthcare sector, optimal pre-dialysis care and the specific treatment recommended for CKD-related metabolic complications are only available to a minority of patients. An example is that erythropoietin use is largely restricted to specialized nephrologist clinics in tertiary level academic hospitals with very limited availability outside of those, at a few regional level hospitals while oral sodium bicarbonate is unavailable countrywide. The challenges of CKD care in our setting reflect the limited number of nephrologists in South Africa, which was estimated at only 1.1 nephrologists per million population (pmp), and the fact that lack of resources has hampered programs for early detection and prevention of CKD (13). Thus, data are urgently needed to guide policies that inform allocation of scarce resources. Studies in the United States (US) found a high prevalence and earlier onset of metabolic abnormalities in blacks , suggesting the need for early screening in this group before estimated glomerular filtration rate (eGFR) is <60 ml/min/1.73m^2 (14, 15). A European study also suggested an association between African ancestry and mineral metabolism disturbance (16). Our hypothesis was that black African patients in our setting manifest CKD-

related metabolic abnormalities at higher eGFR levels than would be expected. Thus, our aim in this study was to determine the prevalence and stage of occurrence of various metabolic abnormalities in a cohort of patients, mostly of African ancestry.

Methods

Study design and setting

This was a cross-sectional study from September 2012 to March 2014 at the General Internal Medicine outpatients' clinic at King Edward VIII Hospital, a 900-bed public-sector regional hospital in Durban, South Africa. The clinic is run by Internal Medicine registrars (residents) under the supervision of consultant physicians (internists). It provides care to adult patients with chronic diseases, mainly hypertension, diabetes, cardiovascular disease, chronic respiratory diseases and HIV, mainly residing in urban and peri-urban Durban areas (Ethekwini Metro). Attendees are often self-referred or referred from primary healthcare facilities and require down-referral back to primary healthcare facilities once deemed to be stable or for further diagnostic work-up followed by referral to various subspecialties, when appropriate.

Participants

All study participants were enrolled for screening for CKD and CKD-related complications following informed consent.

Inclusion criteria were: stable ambulatory patients aged ≥18 years old.

Exclusion criteria were: diagnosis with an intercurrent illness (e.g. infection), malignancy, dialysis-requiring patients and patients requiring in-hospital care.

Data collection

Data collected during clinic consultations were: (i) History: age, gender, prevalent comorbid diseases such as hypertension, diabetes, HIV, current medication; (ii) Physical examination: including blood pressure, anthropometric measurements (weight, height and waist circumference); (iii) Investigations: blood samples were obtained for haemoglobin, serum creatinine, electrolytes, albumin, calcium and phosphate as well as urine specimens for urine albumin: creatinine ratio. All tests were performed onsite at the hospital laboratory, part of the network of the state-funded National Health Laboratory Services (NHLS) in South Africa.

Definitions

CKD was defined as presence, for ≥3 months, of: eGFR <60 ml/min/1.73m^2 and/or dipstick proteinuria and/or abnormal kidney ultrasonography. We used the Modification of Diet in Renal Disease (MDRD) eGFR formula - isotope dilution mass spectrometry (IDMS) version (17) since the NHLS has adopted IDMS-traceable standardized serum creatinine nationwide. We omitted the African-American correction factor, as that was shown to improve its accuracy in South Africans (18, 19). Prevalent disease was based on self-reported history of prior diagnosis, with current medication and clinical records used for verification in all patients. Anaemia was defined as haemoglobin <11 g/dl using the KDIGO target level for treatment while local laboratory values were used for other abnormalities as recommended in the KDIGO guidelines (1). Metabolic acidosis was defined as serum bicarbonate ≤22 mmol/l, hyperphosphataemia as serum phosphate >1.42 mmol/l and hypocalcaemia as corrected calcium <2.15 mmol/l.

Statistical analysis

Data were analysed using Intercooled Stata version 11 (Texas, USA). Continuous data were summarized as mean ± standard deviation or median (25^{th}-75^{th} percentile) for non-normal data and between-group differences evaluated using one way ANOVA or the Kruskal-Wallis test, respectively. Categorical data were expressed as proportions and the chi-square test used for between-group comparisons or Fischer's exact test, where appropriate. Multivariable logistic regression analysis was performed to assess factors associated with each metabolic abnormality and results expressed as the odds ratio with 95% confidence interval [OR (95% CI)]. Statistical significance was considered as a two-tailed $p<0.05$.

Results

Of 307 patients screened, 283 met the inclusion criteria while 24 were excluded for intercurrent illness. Data were missing for serum albumin (3 patients), calcium and phosphate (6 patients, respectively). Overall, CKD was present in 124 (43.8%) patients, including 104 (36.8%) with eGFR <60 ml/min/1.73m^2. Table 1 shows overall patient characteristics and distribution by eGFR level. Hypertension (73.1%) was the commonest comorbidity, followed by diabetes (27.9%) and HIV (19.8%). Other CKD risk factors were uncommon; 40 (14.1%) patients had glomerulonephritis (unrelated to HIV) and 7 (2.5%) had tubulointerstitial disease. The commonest diuretic used was furosemide in 111/186 (59.9%) of patients. Only 29 (10.2%) patients were on calcium supplements and/or vitamin D and/or phosphate binders; 7 (2.5%) patients were taking iron supplements and none were receiving erythropoietin or alkali therapy.

Figure 1 shows that serum bicarbonate and haemoglobin levels decreased significantly once eGFR was <45 ml/min/1.73m^2 while serum phosphate levels increased ($p<0.001$, respectively); serum calcium levels were constant ($p=407$). Prevalent abnormalities were metabolic acidosis

(20.5%), anaemia (19.1%), hyperphosphataemia (13.8%) and hypocalcaemia (5%), with no differences seen with age (Figure 2). Prevalence of each abnormality increased significantly with declining eGFR (Figure 3), with metabolic acidosis and hyperphosphataemia present in 11.6% and 10.1%, respectively, of patients with eGFR levels ≥90 ml/min/1.73m^2. Multivariable logistic regression models showed significant increase in all abnormalities with worsening CKD (Table 2). Furthermore, metabolic acidosis was strongly associated with macroalbuminuria and diuretic use. Diuretic use was also independently associated with lower odds of hypocalcaemia.

Discussion

We observed a high prevalence of CKD-related metabolic abnormalities, which has not been documented previously in sub-Saharan Africa. Metabolic acidosis and hyperphosphataemia were prevalent even at higher eGFR levels; present in ≥10% of patients with eGFR ≥90 ml/min/1.73m^2. The lack of similar studies in Africa hampers appropriate comparison of our findings. Population studies as well as observational studies of selected CKD patients in developed countries estimate that the prevalence of metabolic acidosis and hyperphosphataemia in participants with normal kidney function is 1-9% and 1-7%, respectively (20-24). The higher proportions in this cohort (almost 90% black African), suggest a propensity to develop CKD-related abnormalities earlier. African descendants in the US and Europe were found to have higher prevalence as well as earlier onset of CKD-related abnormalities, mainly hyperparathyroidism, vitamin D deficiency and hyperphosphataemia (14, 15, 25). Our observations support this, suggesting that the association of African ancestry with CKD-related abnormalities is not limited to Africans in the diaspora. Hyperparathyroidism was not evaluated in this study however, it could underlie our findings since metabolic acidosis is associated with

hyperparathyroidism in early CKD (26). Also, parathyroid hormone is involved in phosphate homeostasis early in the course of CKD. However, changes in serum bicarbonate and phosphate levels typically occur when GFR is ≤40 ml/min/1.73m^2 (20, 22). Factors other than race could also explain our findings as the association of black race with elevated phosphate levels has been inconsistent, with some studies finding no relationship between phosphate levels and black race despite the observed positive association with hyperparathyroidism (25, 26). Lower socioeconomic status is one such factor since the study was performed in a public-sector hospital, serving mainly lower socioeconomic patients; however, socioeconomic data were not evaluated. Recent US studies have reported strong association between lower socioeconomic status and hyperphosphataemia, irrespective of race (27, 28).

We found a graded increase in the prevalence of abnormalities with declining eGFR (Figure 3) as observed by others (22, 23, 29, 30). In the cross-sectional analysis of the NephroTest cohort baseline data in France (n = 1038), as GFR fell to <20 ml/min/1.73m^2, prevalence of metabolic acidosis, anaemia and hyperphosphataemia increased to 39%, 41% and 30%, respectively (22). In the more recent BELFRAIL cohort in Belgium (n = 567), anaemia prevalence was 39% and hyperphosphataemia 23%, when eGFR was <30 ml/min/1.73m^2 (30). US population data showed similar estimates when eGFR was <30 ml/min/1.73m^2; metabolic acidosis, anaemia and hyperphosphataemia increased to 36.3%, 41.5% and 27.5%, respectively (24). These proportions were substantially higher in the patient cohort in the present study (72.7%, 69.7% and 48.5%, respectively) but fewer patients in the highest eGFR groups had anaemia (3% and 12% with eGFR ≥90 and 60-89.9, respectively). Anaemia prevalence in early CKD (stages 1-2) was higher (6.2-15.3%) in other studies (24, 29-31). Use of lower haemoglobin cut-off values and the

younger age of our study population might account for this discrepancy. Findings in advanced CKD patients in the present study possibly reflect the lack of treatment of these disorders but could also suggest greater severity in this cohort. It is noteworthy that even where treatment is available, suboptimal management of anaemia and mineral metabolism disturbances has been reported in non-dialysis CKD patients even at academic tertiary nephrology clinics (32-35).

An unexpected finding was the significant independent association of metabolic acidosis with macroalbuminuria. This is contrary to recent studies that found no association between albuminuria and metabolic acidosis (29) or a weak association that was inconsistent within eGFR strata (24). This finding could possibly reflect albuminuria-induced proximal tubular damage and occult systemic inflammation, both of which may be associated with metabolic acidosis (23, 29). Further research is needed into the unexpected association between albuminuria and acidosis in our population. The observed negative association of metabolic acidosis and hypocalcaemia with diuretic use is in keeping with the effects of furosemide, the commonest diuretic in this cohort. This study also confirmed the significance of hypertension, diabetes and HIV as the three commonest CKD risk factors in urban patients as in our previous study at an outreach clinic (36).

Strengths and limitations

The major strengths of this study are the inclusion of participants with a wide range of kidney function, including those with high eGFR levels and the concurrent evaluation of several CKD-related metabolic abnormalities. Using a single centre study, including the same laboratory for all participants was another strength as information bias was minimized. Limitations include the small sample size, with very few patients in the lowest eGFR group. Selection bias as a result of

studying patients at a single centre is another limitation as well as the inability to show causal relationships owing to the cross-sectional design.

Conclusion

CKD-related metabolic abnormalities were common and were observed earlier than expected in this cohort, implying that restricting screening and treatment of these abnormalities to specialized centres in South Africa may not be appropriate. Thus, screening and CKD tertiary prevention strategies need to be extended beyond these centres, especially in our resource-limited setting because treating these abnormalities may retard progression of CKD.

Declarations

Ethics approval and consent to participate

Ethical approval was granted by the University of KwaZulu-Natal Biomedical Research Ethics Committee. All participants provided written informed consent.

Consent for publication

Not applicable.

Availability of data and materials

The data analysed in the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

NDM conceived the study, participated in writing the protocol, data collection and interpretation as well as writing the manuscript. SN co-supervised the research, provided intellectual input into the study protocol and in writing the manuscript. AGHA supervised the research and provided intellectual input into the study protocol as well as in writing the manuscript. All authors read and approved the final manuscript.

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References

1. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO Clinical Practice Guideline for the Evaluation and Management of chronic kidney disease. Kidney Int Suppl. 2012;3(1):1-150.

2. McClellan WM, Jurkovitz C, Abramson J. The epidemiology and control of anaemia among pre-ESRD patients with chronic kidney disease. Eur J Clin Invest. 2005;35 Suppl 3:58-65.

3. Inrig JK, Barnhart HX, Reddan D, Patel UD, Sapp S, Califf RM, et al. Effect of hemoglobin target on progression of kidney disease: a secondary analysis of the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial. Am J Kidney Dis. 2012;60(3):390-401.

4. Covic A, Kothawala P, Bernal M, Robbins S, Chalian A, Goldsmith D. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. Nephrol Dial Transplant. 2009;24(5):1506-23.

5. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006;1(4):825-31.

6. Scialla JJ, Astor BC, Isakova T, Xie H, Appel LJ, Wolf M. Mineral metabolites and CKD progression in African Americans. J Am Soc Nephrol. 2013;24(1):125-35.

7. Shah SN, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. Am J Kidney Dis. 2009;54(2):270-7.

8. Navaneethan SD, Schold JD, Arrigain S, Jolly SE, Wehbe E, Raina R, et al. Serum bicarbonate and mortality in stage 3 and stage 4 chronic kidney disease. Clin J Am Soc Nephrol. 2011;6(10):2395-402.

9. Block GA. Therapeutic interventions for chronic kidney disease-mineral and bone disorders: focus on mortality. Curr Opin Nephrol Hypertens. 2011;20(4):376-81.

10. Phisitkul S, Khanna A, Simoni J, Broglio K, Sheather S, Rajab MH, et al. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. Kidney Int. 2010;77(7):617-23.

11. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int. 2010;78(3):303-9.

12. Susantitaphong P, Sewaralthahab K, Balk EM, Jaber BL, Madias NE. Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. Am J Nephrol. 2012;35(6):540-7.

13. Naicker S, Eastwood JB, Plange-Rhule J, Tutt RC. Shortage of healthcare workers in sub-Saharan Africa: a nephrological perspective. Clin Nephrol. 2010;74 Suppl 1:S129-33.

14. Ibrahim HN, Wang C, Ishani A, Collins AJ, Foley RN. Screening for chronic kidney disease complications in US adults: racial implications of a single GFR threshold. Clin J Am Soc Nephrol. 2008;3(6):1792-9.

15. Gutierrez OM, Isakova T, Andress DL, Levin A, Wolf M. Prevalence and severity of disordered mineral metabolism in Blacks with chronic kidney disease. Kidney Int. 2008;73(8):956-62.

16. Ureña-Torres P, Metzger M, Haymann JP, Karras A, Boffa J-J, Flamant M, et al. Association of kidney function, vitamin D deficiency, and circulating markers of mineral and bone disorders in CKD. Am J Kidney Dis. 2011;58(4):544-53.

17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation for the Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-70.

18. Madala ND, Nkwanyana N, Dubula T, Naiker IP. Predictive performance of eGFR equations in South Africans of African and Indian ancestry compared with (99m)Tc-DTPA imaging. Int Urol Nephrol. 2012;44(3):847-55.

19. Van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ. Estimating glomerular filtration rate in black South Africans by use of the Modification of Diet in Renal Disease and Cockcroft-Gault equations. Clin Chem. 2008;54(7):1197-202.

20. Levin A, Bakris G, Molitch M, Smulders M, Tian J, Williams L, et al. Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. Kidney Int. 2007;71(1):31-8.

21. Foley RN, Wang C, Ishani A, Ibrahim HN, Collins AJ. Creatinine-Based Glomerular Filtration Rates and Microalbuminuria for Detecting Metabolic Abnormalities in US Adults: The National Health and Nutrition Examination Survey 2003–2004. Am J Nephrol. 2008;28(3):431.

22. Moranne O, Froissart M, Rossert J, Gauci C, Boffa J-J, Haymann JP, et al. Timing of onset of CKD-related metabolic complications. J Am Soc Nephrol. 2009;20(1):164-71.

23. Eustace JA, Astor B, Muntner PM, T ALP I, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. Kidney Int. 2004;65(3):1031-40.

24. Inker LA, Coresh J, Levey AS, Tonelli M, Muntner P. Estimated GFR, albuminuria, and complications of chronic kidney disease. J Am Soc Nephrol. 2011;22:2322–31.

25. Ennis J, Worcester E, Coe F. Contribution of calcium, phosphorus and 25-hydroxyvitamin D to the excessive severity of secondary hyperparathyroidism in African-Americans with CKD. Nephrol Dial Transplant. 2012;27:2847–53.

26. de Boer IH, Gorodetskaya I, Young B, Hsu C-y, Chertow GM. The severity of secondary hyperparathyroidism in chronic renal insufficiency is GFR-dependent, race-dependent, and associated with cardiovascular disease. J Am Soc Nephrol. 2002;13(11):2762-9.

27. Gutiérrez OM, Anderson C, Isakova T, Scialla J, Negrea L, Anderson AH, et al. Low socioeconomic status associates with higher serum phosphate irrespective of race. J Am Soc Nephrol. 2010;21(11):1953-60.

28. Gutiérrez OM, Isakova T, Enfield G, Wolf M. Impact of poverty on serum phosphate concentrations in the Third National Health and Nutrition Examination Survey. J Ren Nutr. 2011;21(2):140-8.

29. Viswanathan G, Sarnak MJ, Tighiouart H, Muntner P, Inker LA. The association of chronic kidney disease complications by glomerular filtration rate and albuminuria: a cross-sectional analysis. Clin Nephrol. 2013;80(1):29-39.

30. Van Pottelbergh G, Vaes B, Jadoul M, Matheï C, Wallemacq P, Degryse J-M. The prevalence and detection of chronic kidney disease (CKD)-related metabolic complications as a function of estimated glomerular filtration rate in the oldest old. Arch Gerontol Geriatr. 2012;54(3):e419-e25.

31. Stauffer ME, Fan T. Prevalence of anemia in chronic kidney disease in the United States. PLoS One. 2014;9(1):e84943.

32. Murray BM, Malireddi K, Vavilala V. Delivery of predialysis care in an academic referral nephrology practice. Ren Fail. 2005;27(5):571-80.

33. Weisbord SD, Fried LF, Mor MK, Resnick AL, Kimmel PL, Palevsky PM, et al. Associations of race and ethnicity with anemia management among patients initiating renal replacement therapy. J Natl Med Assoc. 2007;99(11):1218-26.

34. Kumar N, Lindberg J, David K, Morris J, Menoyo J. Real-world doxercalciferol treatment in SHPT CKD stage 3 and 4: an analysis of change in iPTH and accordance to KDOQI recommendations. Am J Nephrol. 2009;29(2):71-8.

35. Minutolo R, Locatelli F, Gallieni M, Bonofiglio R, Fuiano G, Oldrizzi L, et al. Anaemia management in non-dialysis chronic kidney disease (CKD) patients: a multicentre prospective study in renal clinics. Nephrol Dial Transplant. 2013;28(12):3035-45.

36. Madala ND, Thusi GP, Assounga AG, Naicker S. Characteristics of South African patients presenting with kidney disease in rural KwaZulu-Natal: a cross-sectional study. BMC Nephrol. 2014;15(1):61.

Figures

Table 1. Patient characteristics and distribution by estimated glomerular filtration rate

Parameter	Overall (n = 283)	eGFR >90 (n = 69)	eGFR 60-89.9 (n = 110)	eGFR <60 (n = 104)	p-value
Age (years)	51.3 ± 14.5	42.8 ± 12.9	51.9 ± 13.9	56.5 ± 13.6	<0.001
Female (%)	62.5	59.4	62.7	64.4	0.80
African (%)	86.2	85.5	82.7	90.4	0.25
Comorbidities					
Hypertension (%)	73.1	53.6	72.7	86.5	<0.001
Diabetes (%)	27.9	23.2	22.7	36.5	0.05
HIV (%)	19.8	20.3	22.7	16.4	0.51
Other CKD risk factors (%)	16.6	8.7	17.3	21.2	0.09
Diuretics (%)	65.7	47.8	67.3	76	0.001
#ACE inhibitors/ARBs (%)	56.9	42	60.9	62.5	0.02
Calcium channel blockers (%)	31.1	11.6	28.2	47.1	<0.001
Waist circumference (cm)	100.1 ± 14.9	98 ± 15.7	101 ± 14.6	100.5 ± 14.7	0.45
Body mass index (kg/m^2)	30.8 ± 7.4	30.2 ± 7.5	30.8 ± 7.3	31.1 ± 7.4	0.70
Systolic BP (mmHg)	127.2 ± 21.7	119.7 ± 19.9	124 ± 19.1	135.6 ± 22.7	<0.001
Diastolic BP (mmHg)	73.7 ± 15.3	70.9 ± 13.6	73.8 ± 15	75.3 ± 16.5	0.18
*Serum creatinine (µmol/l)	84 (68-110)	59 (54-72)	77.5 (59- 89)	126 (99- 211)	<0.001
*MDRD-eGFR (ml/min/1.73m^2)	71 (51-89)	103 (97-113)	75 (69- 81)	43.5 (25.5-53)	<0.001
*CKD-EPI-eGFR (ml/min/1.73m^2)	78 (55-98)	111 (102-118)	83 (76-90)	47 (26.5-57)	<0.001
Macroalbuminuria (%)	20.9	10.1	11.8	37.5	<0.001

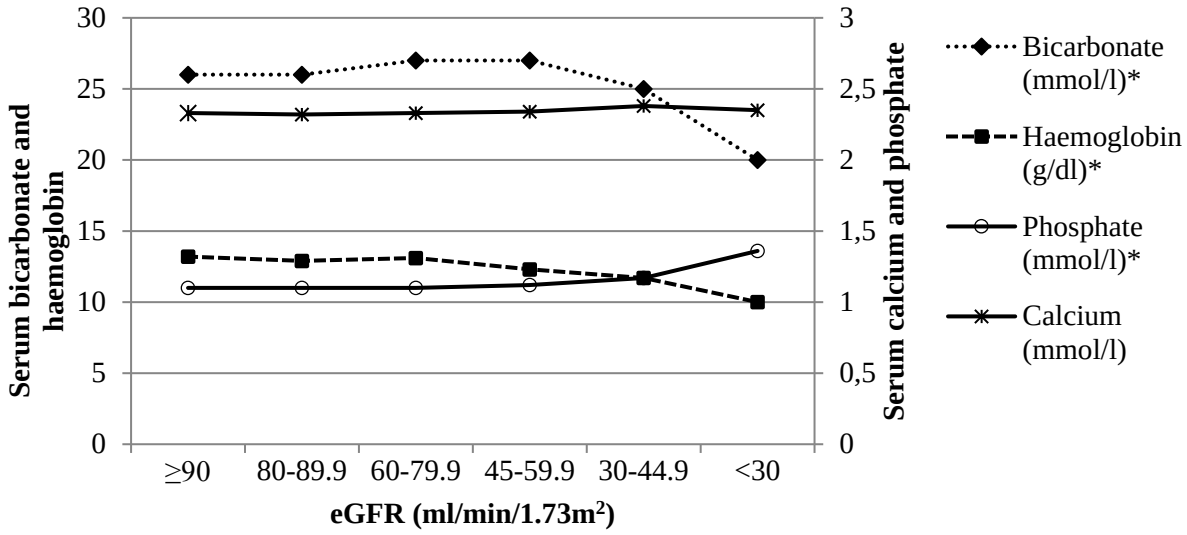
#Includes 7 patients on ARBs, *Median (25th-75th percentile). eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; BP, blood pressure; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease in Epidemiology.

Table 2. Multivariable logistic regression models showing adjusted odds ratios (95% confidence intervals) for each metabolic abnormality

Parameter	Metabolic acidosis	Anaemia	Hyperphosphataemia	Hypocalcaemia
Age	0.99 (0.96-1.02)	1.0 (0.97-1.04)	0.98 (0.95-1.01)	0.96 (0.91-1.01)
Male gender	0.90 (0.41-1.99)	0.54 (0.22-1.30)	0.48 (0.20-1.16)	0.60 (0.16-2.23)
Hypertension	1.34 (0.43-4.12)	2.54 (0.70-9.25)	1.41 (0.39-5.09)	7.37 (0.86-62.54)
Diabetes	1.25 (0.56-2.77)	1.10 (0.48-2.52)	0.66 (0.26-1.70)	0.21 (0.03-1.43)
HIV	1.59 (0.49-5.23)	2.97 (0.88-9.98)	0.42 (0.10-1.66)	1.02 (0.14-7.40)
Glomerulonephritis	1.57 (0.47-5.18)	1.06 (0.30-3.78)	2.79 (0.75-10.36)	1.77 (0.23-13.91)
Tubulointerstitial disease	0.76 (0.13-4.57)	1.70 (0.35-8.34)	0.30 (0.03-3.01)	1.55 (0.11-20.98)
Diuretic use	**0.21 (0.08-0.54)***	0.82 (0.31-2.17)	1.21 (0.44-3.32)	**0.14 (0.03-0.59)***
ACE inhibitor use	1.06 (0.45-2.48)	0.63 (0.28-1.41)	1.10 (0.46-2.64)	2.47 (0.52-11.84)
Waist circumference	0.99 (0.94-1.03)	0.99 (0.94-1.04)	1.02 (0.99-1.07)	1.04 (0.95-1.14)
Body mass index	0.99 (0.90-1.10)	1.04 (0.94-1.14)	0.90 (0.81-1.01)	0.88 (0.72-1.06)
Macroalbuminuria	**5.05 (2.02-12.6)****	2.02 (0.83-4.93)	0.95 (0.36-2.48)	3.06 (0.62-15.12)
Worsening CKD stage	**1.92 (1.40-2.61)****	**2.41 (1.74-3.35)****	**2.09 (1.48-2.93)****	**1.86 (1.09-3.18)^**

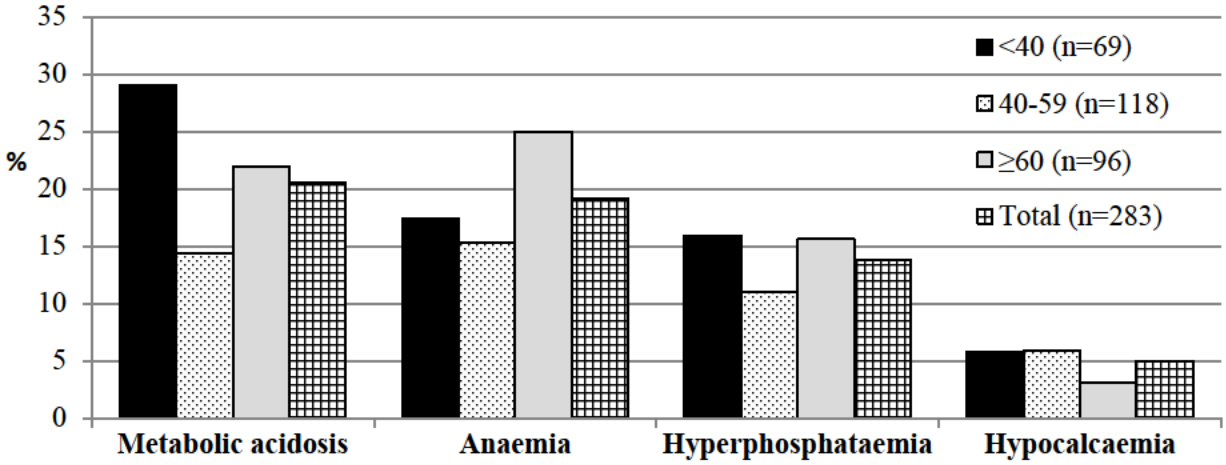
Significant relationships are highlighted in bold text; **p≤0.001, *p<0.01, ^p<0.05. ACE, angiotensin converting enzyme; CKD, chronic kidney disease.

Figure 1. Median values for bicarbonate, haemoglobin, calcium and phosphate according to estimated glomerular filtration rate



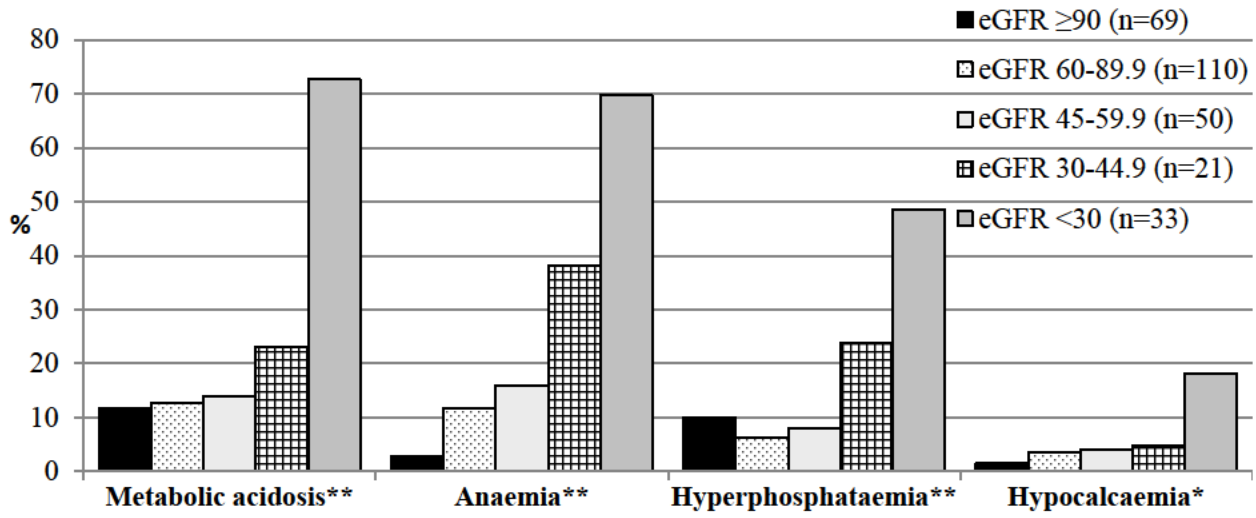
*p<0.001; eGFR, estimated glomerular filtration rate.

Figure 2. Prevalence of metabolic abnormalities and distribution by age group



n, number; age groups in years.

Figure 3. Prevalence of metabolic abnormalities by estimated glomerular filtration rate



**p<0.001, *p<0.05. n, number; eGFR, estimated glomerular filtration rate.

CHAPTER 5

RELATIONSHIP BETWEEN BODY COMPOSITION AND GLOMERULAR FILTRATION RATE IN SOUTH AFRICANS WITH NON-DIALYSIS CHRONIC KIDNEY DISEASE

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TITLE:

RELATIONSHIP BETWEEN BODY COMPOSITION AND GLOMERULAR FILTRATION RATE IN SOUTH AFRICANS WITH NON-DIALYSIS CHRONIC KIDNEY DISEASE

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Abstract

Background

Protein energy wasting (PEW) is a significant contributor to adverse outcomes in chronic kidney disease (CKD), which is under-recognized in Africa. Markers of PEW include changes in body composition and biochemical parameters. We analysed the relationship of body composition and glomerular filtration rate (GFR) in non-dialysis CKD patients.

Methods

This cross-sectional study assessed body composition using weight-based anthropometry and dual X-ray absorptiometry in 70 adults with GFR ≥60 and <60 ml/min/1.73m^2. Measured GFR (mGFR) with technicium-99m-diethylenetriaminepentaacetic acid was performed. We evaluated lean and fat mass correlation with other variables and determined associated factors using linear regression models.

Results

Body mass index decreased significantly and waist-to-height ratio marginally with mGFR. Whole body and regional lean as well as fat mass decreased with mGFR; with strong correlation observed in males ($r \geq 0.5$, $p \leq 0.02$ for lean and fat mass with mGFR). Lean mass in males was associated with HIV, serum albumin, haemoglobin and mGFR in the univariate analysis while serum albumin remained a significant independent factor on multivariate analysis (standardized β-coefficient 0.43, p=0.03). Fat mass was associated with HIV, haemoglobin and mGFR in males; association with mGFR persisted in the adjusted model (standardized β-coefficient 0.63, P=0.04). In females, fat mass was associated with age and serum bicarbonate and age remained a significant independent factor (standardized β-coefficient 0.49, p=0.005) on multivariable analysis.

Conclusion

Males showed greater lean and fat mass loss at lower mGFR than females. Nutritional surveillance and intervention might be needed in males as early as stage 3b CKD in our patients.

Keywords: African, body composition, chronic kidney disease, fat mass, lean mass, glomerular filtration rate

Background

Protein energy wasting (PEW), characterized by loss of body protein and fat, is a major risk factor for poor outcomes in chronic kidney disease (CKD) (1, 2). The prevalence of PEW in dialysis patients is 18-75% (3). Data for earlier CKD stages are fewer but suggest that PEW might start early in CKD. A cross-sectional study of participants in the Modification of Diet in Renal Disease (MDRD) study found that protein energy nutritional status declined progressively with decreasing glomerular filtration rate (GFR) (4). More recent studies have reported PEW in 18-25% of patients with early to moderate CKD (5). Methods used for diagnosis of PEW in patients include evaluation of body mass and composition, using weight-based anthropometric measures, skin and muscle anthropometric measures, total body elements as well as imaging, energy-beam or electrical current methods (5). Anthropometry, bioelectrical impedance analysis and dual X-ray absorptiometry (DEXA) are body composition analysis techniques that are readily applicable in clinical settings as gold standard methods are not practical for routine use, with DEXA shown to have high accuracy and precision (6). Prevalence data on PEW in non-dialysis CKD are lacking in South Africa. A study in Durban (South Africa) in the late 1990s found that protein malnutrition was highly prevalent in patients receiving continuous ambulatory peritoneal dialysis (CAPD), reported in 76.2% of patients and males as well as younger patients had the greatest risk, while inadequate dietary protein intake was the most important factor (7). Studies in healthy volunteers showed that black/indigenous South Africans had lower dietary protein intake than Americans and Caucasian South Africans (8). These data suggest a higher risk for PEW in the local South African population, with prevalence of PEW and/or its markers likely to be high in earlier CKD stages. Thus, we sought to investigate this hypothesis by evaluating body composition and its relationship to GFR in non-dialysis CKD patients.

Methods

Patients and setting

We recruited participants in a screening study for CKD and related metabolic abnormalities at the outpatient clinic at King Edward VIII Hospital, a public-sector hospital in Durban. Eligible patients were adults, aged ≥18 years old and with stages 3-5 CKD, using estimated GFR (eGFR). GFR estimation was based on the MDRD equation (9) using standardized serum creatinine,

which is reported routinely by the state-funded National Health Laboratory Services in South Africa. Of 104 prevalent CKD patients that were eligible to participate, 70 patients who were able to undergo radioisotope GFR as well as DEXA within 2-4 weeks of the initial screening were included in this cross-sectional study. Unstable patients with an intercurrent infection and/or malignancy as well as those requiring dialysis or hospitalization were excluded. The study was approved by the Biomedical Research Ethics Committee of the University of KwaZulu-Natal and written informed consent was obtained from all participants.

Demographic, clinical and laboratory data

Age, gender, ethnicity, prevalent comorbidities and blood pressure were documented. Laboratory tests done were: serum creatinine, urea, electrolytes, serum albumin, total cholesterol, serum triglycerides and C-reactive protein.

Anthropometry

Measurements were taken for body weight (kg), height (cm) and waist circumference (cm). Body mass index (BMI) was calculated as weight/height^2 (kg/m^2) and waist-to-height ratio (WHtR) determined as waist (cm)/height (cm).

Body composition data by DEXA

Scans were performed using a total body scanner (QDR-200 Hilogic, Waltham, MA) generating X-rays at two energy levels (40 and 70 kVp). Participants were asked to lie down on the device and a series of transverse scans made from head to toe at 1 cm intervals. Standard compartmentalization of the body was done, allowing analysis of whole body, as well as regional (trunk and limbs) lean and fat mass with bone mineral content. Percent body fat (%fat) was derived using computer algorithms provided by the manufacturer.

Renal function measurement

Radioisotope measured GFR (mGFR) was obtained following intravenous injection of 100 µCi of technicium-99m-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) according to a standard protocol at the Medical Physics Department at our hospital.

Definitions:

We defined CKD as the presence, for ≥3 months, of estimated glomerular filtration rate (eGFR) <60 ml/min/1.73m^2 and/or albuminuria (≥3 mg/mmol) and/or structural kidney abnormalities on ultrasonography according to the Kidney Disease Improving Global Outcomes (KDIGO) Guidelines (10). Hypertension was defined as ambulatory SBP > 140 and/or DBP > 90 (11) and/or current use of antihypertensive medication. Diabetes was defined as random blood sugar ≥11.1 mmol/l and/or glycated haemoglobin A_{1c} ≥6.0% (12) and/or use of antidiabetic treatment. Glomerulonephritis was based on histological diagnosis. A positive HIV test and/or use of antiretroviral treatment were taken as evidence for HIV infection. Hypoalbuminaemia was defined as serum albumin <35 g/l, using the cut-off value at our hospital laboratory that is also used in KDIGO Guidelines (10) and serum albumin <38 g/l as in PEW criteria (2).

Statistical analysis

Data were analysed using Intercooled Stata version 11 (Texas, USA). Categorical data were expressed as proportions and Fisher's exact test was used for between-group comparisons. Continuous data were summarized as mean ± standard deviation or median (25^{th}-75^{th} percentile) with between-group differences evaluated using the t-test or Mann-Whitney test, respectively and where applicable, 2-factorial multivariate analysis of variance (MANOVA) was employed. Pearson's correlation coefficients were used to assess the correlation between DEXA measurements and other variables. Multivariate linear regression analysis was performed to assess factors associated with lean and fat mass. Covariates were included in the multivariate model when significant on univariate analysis. Non-normal variables were log transformed and the log included as the dependent variable. Statistical significance was considered as $P<0.05$.

Results

Patient characteristics

Measured GFR was <60 ml/min/1.73 m^2 in 70.2% of patients (68.4% of males and 70.8% of females). Comorbid diseases included hypertension (90%) of patients, cardiovascular disease (CVD) (37.1%), diabetes (32.7%), non-HIV glomerulonephritis (11.4%), HIV (10%) and tubulointerstitial diseases (4.3%); all with similar gender distribution. Table 1 shows the patient characteristics. Obesity was common overall, BMI ≥30 kg/m^2 in 31 (44.3%) patients, however

females had higher BMI, WHtR and body fat. BMI was <23 kg/m^2 in 9 patients (5 males) and none had <10% body fat. BMI decreased significantly and WHtR marginally with mGFR. Whole body as well as regional lean and fat mass were lower in those with mGFR <60 ml/min/1.73 m^2, particularly in males, with significant interaction found between male gender and mGFR. Using serum albumin <35 g/l, 20 (28.6%) patients had hypoalbuminaemia, which increased to 41 (58.6%) patients when the level of <38 g/l was used; with no gender difference. The lower limb lean mass seen with lower mGFR in males was significant in the legs (Figure 1), while fat mass was lower in the arms (Figure 2). There were no differences in lean and fat mass with mGFR in females.

Relationship between body composition by DEXA and other study variables in the whole cohort

Table 2 shows the correlation matrix of body composition measures by DEXA with other study variables. Whole body and regional lean mass correlated with anthropometry (r=0.3 to r=0.9, p<0.001 for all), serum albumin (r=0.3, p=0.01 to p=0.006), haemoglobin (r≥0.3, p=0.001 to p=0.007) and total cholesterol (r=-0.3, p=0.03). Whole body as well as regional fat mass and %fat correlated positively with age (r≥0.3, p≤0.01), anthropometry (r≥0.7, p<0.001 for whole as well as regional body fat with BMI and WHtR) and serum bicarbonate (r=0.3, p≤0.01); similar correlation of haemoglobin with trunk fat was also observed. Neither lean nor fat mass correlated with mGFR and CRP while fat mass correlated weakly with serum creatinine.

Correlation and multivariate regression analyses in males and females

When males and females were analysed separately (data not shown), whole body and regional lean as well as fat mass in males correlated strongly with mGFR (all r≥0.5, p≤0.02) and haemoglobin (r≥0.6, p=0.01 to p=0.007, respectively). In females, there was positive correlation of whole body as well as regional fat mass with age (r≥0.3, p=0.02 to p=0.003, respectively) and with serum bicarbonate (r≥0.3, p=0.02 to p=0.003, respectively). In univariate analyses, HIV infection, serum albumin, haemoglobin and mGFR were significantly associated with lean mass in males (Table 3). Serum albumin remained a significant factor after adjusting for other significant variables. None of the variables analysed were associated with lean body mass in females. Factors associated with whole body fat mass on univariate analysis were age and serum bicarbonate in females while HIV infection, haemoglobin as well as mGFR were significant

factors in males (Table 4). Age remained significant in females after adjusting for other significant variables while in males there was borderline association of whole body fat with mGFR (P=0.04).

Discussion

We evaluated body composition in a cohort of non-dialysis CKD patients. The major finding was that males had significantly lower whole body lean and fat mass with lower mGFR, involving trunk more than limb lean mass, which was not found in females. Our results support the gender difference observed in previous local CAPD studies of greater risk for malnutrition in males (7). These results are significant because mean mGFR in males with mGFR <60 ml/min/1.73 m^2 was 36.3 ± 9.1 ml/min/1.73 m^2, suggesting that significant loss of lean and fat mass might begin in stage 3b CKD in males in our setting. This is the first report of such observations in non-dialysis CKD patients in Africa. The association of male gender with lean mass loss has not been consistently reported. Males in the cross-sectional MDRD study had lower lean mass at lower GFR levels but not females (4). A more recent longitudinal study also found lean mass loss with worsening GFR in males that was not seen in females (13). In contrast, lean mass depletion was greater in female non-dialysis CKD patients in the cross-sectional study by Woodrow et al.; also of note is that there was greater limb than trunk lean tissue wasting in that study (14). Thus, the finding of significantly lower trunk than limb lean mass in the present study differs and needs further evaluation. Females were also more likely to have PEW in a recent study of non-dialysis CKD patients in Brazil (15). Loss of lean mass and fat mass are among key indicators of PEW, particularly if shown over time (3-6 months) on repeated evaluation (2). Dietary intake is one of the PEW components that we did not evaluate, which we would expect to show low protein intake based on published data. Surrogates of nutritional status assessed were serum albumin and total cholesterol, which are both included in PEW criteria (2). Significant positive correlation of serum albumin with whole body and regional lean mass as well as the robust association of lower lean mass with lower serum albumin in the adjusted model could further imply greater nutritional risk in males. However, positive correlation of lean mass with total cholesterol would then have been expected whereas the observed inverse correlation and lack of significant association in the multivariate regression model are not in keeping. Reports of the relationship of serum albumin to lean mass are conflicting as some showed positive correlation (16) whereas others found none

(17, 18). While lean mass in males in this study was also associated with HIV, haemoglobin and mGFR on univariate analysis, these associations were eliminated in the adjusted model, which is most likely because the covariates are associated with kidney function. Lack of association of lean mass with serum bicarbonate and CRP were unexpected findings, since there is conclusive evidence linking lean mass loss with metabolic acidosis and inflammation. Both are prevalent in CKD with metabolic acidosis present in 1-40% (19-22) and inflammation in 30-60% of non-dialysis CKD patients (1, 19, 23); their role as mediators of muscle protein catabolism leading to muscle wasting has been discussed in recent reviews (3, 24, 25). Lack of association of lean mass with serum bicarbonate in our study probably reflects the normal serum bicarbonate levels (mean 23.9 ± 3.8 mmol/l), while absence of an association with CRP could relate to the predominance of black/African subjects (>90%). Data on racial differences on the effect of inflammation are emerging, with inflammation shown to mediate the relationship between lean mass loss and kidney function in white but not in black males (13). Similarly, African ancestry was recently shown to modify the relationship between inflammation and fat mass, with stronger association observed in Caucasian compared to African Americans (26). Other potential explanations for the absence of a relationship between CRP and lean or fat mass in our cohort could be the high prevalence of inflammation (CRP ≥5 mg/l in 55.7% of patients) and obesity, which might also explain the prevalence of hypoalbuminaemia. Adipose tissue is well-established as a source of proinflammatory mediators, thus obesity and fat mass have been associated with inflammation in patients with various stages of CKD in addition to inflammation that occurs with CKD (26-28). Correlation of CRP with mGFR has also been inconsistent, with some reporting no correlation (29) as in the current study, while others found an inverse association (30, 31).

The major strength of this study is use of ^{99m}Tc-DTPA mGFR because a suitable eGFR equation for sub-Saharan Africans has not yet been developed and available equations have shown poor predictive performance (32, 33). Our results must be interpreted in the context of the major limitations of this study. Firstly, the cross-sectional design precludes any causal relationship from observed associations and limits the extent to which body composition findings can be interpreted as PEW markers. The sample size was small and based largely on convenience since both ^{99m}Tc-DTPA mGFR and DEXA were not required for patient care, thus the study may not

have been sufficiently powered to show significant associations. Lastly, use of a single inflammatory marker may also be a potential limitation; however, CRP is a well-established and the best studied inflammatory marker (34).

Conclusion

We conclude that male CKD patients might have greater whole body and lean as well as fat mass loss at lower mGFR than females in this study population, which may be observed from as early as stage 3b CKD. Implications are that nutritional surveillance and intervention might be needed early in the course of CKD in males, requiring training of primary care practitioners since CKD is largely managed by non-nephrologists in our setting, as in others with limited resources. Further research is needed to assess longitudinal body composition changes as well as dietary and socioeconomic factors.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

References

1. Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int. 1999;55(5):1899-911.

2. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73(4):391-8.

3. Dukkipati R, Kopple JD. Causes and prevention of protein-energy wasting in chronic kidney failure. Semin Nephrol. 2009;29(1):39-49.

4. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int. 2000;57(4):1688-703.

5. Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy. Am J Clin Nutr. 2013;97(6):1163-77.

6. Woodrow G. Body composition analysis techniques. Perit Dial Int. 2007;27:S245–S9.

7. Naicker S. Nutritional problems associated with end-stage renal disease in the developing world. Artif Organs. 2002;26(9):757-9.

8. O'Keefe SJ, Chung D, Mahmoud N, *et al*. Why do African Americans get more colon cancer than Native Africans? J Nutr. 2007;137(1 Suppl):175S-82S.

9. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation for the Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-70.

10. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO Clinical Practice Guideline for the Evaluation and Management of chronic kidney disease. Kidney Int Suppl. 2012;3(1):1-150.

11. Seedat YK, Rayner BL. South African Hypertension Guideline 2011. S Afr Med J. 2012;102:57-84.

12. Amod AA, Ascot-Evans BH, Berg GI. The 2012 SEMDSA guidelines for the management of type 2 diabetes. JEMDSA. 2012;17:S1-95.

13. Fried LF, Boudreau R, Lee JS, Chertow G, Kurella-Tamura M, Shlipak MG, et al. Kidney function as a predictor of loss of lean mass in older adults: health, aging and body composition study. J Am Geriatr Soc. 2007;55(10):1578-84.

14. Woodrow G, Oldroyd B, Turney J, Tompkins L, Brownjohn A, Smith M. Whole body and regional body composition in patients with chronic renal failure. Nephrol Dial Transplant. 1996;11(8):1613-8.

15. Amparo FC, Kamimura MA, Molnar MZ, Cuppari L, Lindholm B, Amodeo C, et al. Diagnostic validation and prognostic significance of the Malnutrition-Inflammation Score in nondialyzed chronic kidney disease patients. Nephrol Dial Transplant. 2014:gfu380.

16. McIntyre CW, Selby NM, Sigrist M, Pearce LE, Mercer TH, Naish PF. Patients receiving maintenance dialysis have more severe functionally significant skeletal muscle wasting than patients with dialysis-independent chronic kidney disease. Nephrol Dial Transplant. 2006;21(8):2210-6.

17. Heimburger O, Qureshi AR, Blaner WS, Berglund L, Stenvinkel P. Hand-grip muscle strength, lean body mass, and plasma proteins as markers of nutritional status in patients with chronic renal failure close to start of dialysis therapy. Am J Kidney Dis. 2000;36(6):1213-25.

18. Majchrzak KM, Pupim LB, Sundell M, Ikizler TA. Body composition and physical activity in end-stage renal disease. J Ren Nutr. 2007;17(3):196-204.

19. Eustace JA, Astor B, Muntner PM, T ALP I, Coresh J. Prevalence of acidosis and inflammation and their association with low serum albumin in chronic kidney disease. Kidney Int. 2004;65(3):1031-40.

20. Moranne O, Froissart M, Rossert J, Gauci C, Boffa J-J, Haymann JP, et al. Timing of onset of CKD-related metabolic complications. J Am Soc Nephrol. 2009;20(1):164-71.

21. Inker LA, Coresh J, Levey AS, Tonelli M, Muntner P. Estimated GFR, albuminuria, and complications of chronic kidney disease. J Am Soc Nephrol. 2011;22:2322–31.

22. Viswanathan G, Sarnak MJ, Tighiouart H, Muntner P, Inker LA. The association of chronic kidney disease complications by glomerular filtration rate and albuminuria: a cross-sectional analysis. Clin Nephrol. 2013;80(1):29-39.

23. Pupim LB, Heimburger O, Qureshi AR, Ikizler TA, Stenvinkel P. Accelerated lean body mass loss in incident chronic dialysis patients with diabetes mellitus. Kidney Int. 2005;68(5):2368-74.

24. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr. 2013;23(2):77-90.

25. Ikizler TA, Cano NJ, Franch H, Fouque D, Himmelfarb J, Kalantar-Zadeh K, et al. Prevention and treatment of protein energy wasting in chronic kidney disease patients: a consensus statement by the International Society of Renal Nutrition and Metabolism. Kidney Int. 2013;84(6):1096-107.

26. Wing MR, Yang W, Teal V, Navaneethan S, Tao K, Ojo A, et al. Race modifies the association between adiposity and inflammation in patients with chronic kidney disease: findings from the chronic renal insufficiency cohort study. Obesity. 2014;22(5):1359-66.

27. Beddhu S, Kimmel PL, Ramkumar N, Cheung AK. Associations of metabolic syndrome with inflammation in CKD: results From the Third National Health and Nutrition Examination Survey (NHANES III). Am J Kidney Dis. 2005;46(4):577-86.

28. Ramos LF, Shintani A, Ikizler TA, Himmelfarb J. Oxidative stress and inflammation are associated with adiposity in moderate to severe CKD. J Am Soc Nephrol. 2008;19(3):593-9.

29. Oberg BP, McMenamin E, Lucas FL, McMonagle E, Morrow J, Ikizler TA, et al. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int. 2004;65(3):1009-16.

30. Nerpin E, Helmersson-Karlqvist J, Risérus U, Sundström J, Larsson A, Jobs E, et al. Inflammation, oxidative stress, glomerular filtration rate, and albuminuria in elderly men: a cross-sectional study. BMC Res Notes. 2012;5(1):537.

31. Gupta J, Mitra N, Kanetsky PA, Devaney J, Wing MR, Reilly M, et al. Association between albuminuria, kidney function, and inflammatory biomarker profile in CKD in CRIC. Clin J Am Soc Nephrol. 2012;7(12):1938-46.

32. Van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ. Estimating glomerular filtration rate in black South Africans by use of the Modification of Diet in Renal Disease and Cockcroft-Gault equations. Clin Chem. 2008;54(7):1197-202.

33. Madala ND, Nkwanyana N, Dubula T, Naiker IP. Predictive performance of eGFR equations in South Africans of African and Indian ancestry compared with (99m)Tc-DTPA imaging. Int Urol Nephrol. 2012;44(3):847-55.

34. Miyamoto T, Carrero JJ, Stenvinkel P. Inflammation as a risk factor and target for therapy in chronic kidney disease. Curr Opin Nephrol Hypertens. 2011;20(6):662-8.

Table 1. Overall patient characteristics with distribution by gender and measured glomerular filtration level.

Parameter	Total	Females (n=48)		Males (n=22)		Gender versus mGFR	p-value
		mGFR≥60 ml/min/1.73 m^2	mGFR<60 ml/min/1.73 m^2	mGFR≥60 ml/min/1.73 m^2	mGFR<60 ml/min/1.73 m^2		
	n=70	n=14	n=34	n=9	n=13		
Demographic data							
Age (years)	57.9 ± 13.2	57.0 ± 13.5	58.2 ± 13.2	57.0 ± 14.0	56.8 ± 14.1	NS	0.97
African, n(%)	64 (91.4)	12 (85.7)	33 (97.1)	7 (77.8)	12 (92.3)	NS	0.26
Body composition data							
BMI (kg/m^2)	30.4 ± 6.9	33.4 ± 7.2	31.1 ± 6.8	30.9 ± 7.2	25.0 ± 3.2	NS	0.01
[a]Waist-to-height ratio	0.61 ± 0.09	0.65 ± 0.09	0.62 ± 0.09	0.61 ± 0.10	0.55 ± 0.04	NS	0.04
[a]Waist circumference (cm)	99.3 ± 13.6	103.4 ± 14.1	99.0 ± 14.7	103.0 ± 13.2	93.0 ± 8.5	NS	0.20
Whole body lean mass (kg)	46.4 ± 8.0	44.8 ± 7.7	43.7 ± 6.1	56.8 ± 9.0	48.1 ± 6.5	A*AxB[#]	<0.001
Whole body LBMI (kg/m^2)	17.5 ± 2.6	17.6 ± 2.6	17.0 ± 2.2	19.7 ± 3.5	17.0 ± 1.8	A[#]	0.03
Whole body fat mass (kg)	33.6 ± 13.1	40.8 ± 14.3	35.8 ± 12.3	30.2 ± 12.4	22.6 ± 5.9	A[#]	0.001
Whole body FBMI (kg/m^2)	12.8 ± 5.3	16.0 ± 5.3	13.9 ± 4.9	10.7 ± 5.0	7.9 ± 1.8	Aˆ	0.008
Whole body fat percent (%)	40.8 ± 9.0	46.6 ± 6.9	43.9 ± 7.1	33.3 ± 8.5	31.5 ± 5.2	A*	<0.001
Trunk lean mass (kg)	22.3 ± 3.8	21.2 ± 3.1	21.1 ± 3.0	27.0 ± 4.3	23.2 ± 3.3	A*AxB[#]	<0.001
Trunk fat mass (kg)	15.9 ± 6.5	19.1 ± 6.7	16.3 ± 6.4	15.8 ± 6.7	11.3 ± 3.7	NS	0.01
Trunk fat percent (%)	40.1 ± 9.7	46.1 ± 7.9	42.1 ± 8.8	35.0 ± 9.9	31.9 ± 7.1	A[#]	<0.001
Limb lean mass	20.7 ± 4.2	20.3 ± 4.5	19.3 ± 3.2	25.8 ± 4.5	21.3 ± 3.3	A*	0.001
Limb fat mass	16.6 ± 7.2	20.7 ± 8.2	18.5 ± 6.4	13.2 ± 5.9	10.2 ± 2.5	Aˆ	0.007
Renal and laboratory data							
[b]mGFR (ml/min/1.73 m^2)	48.9 ± 18.8	73.2 ± 12.0	40.1 ± 12.3	68.7 ± 5.3	36.3 ± 9.1	B*	<0.001
[c]Serum creatinine (µmol/l)	120 (94-185)	94 ± 86-98)	128 (100-185)	121 (115-137)	210 (129-236)	B[#]	0.03
[c]Blood urea (mmol/l)	7.3 (4.9-10.4)	6.3 (4.3-7.1)	7.4 (5.7-12.8)	4.9 (4.3-9.6)	12.4 (8.1-14.7)	B[#]	0.007
Serum bicarbonate (mmol/l)	23.9 ± 3.8	25.9 ± 3.4	23.3 ± 3.9	23.4 ± 4.1	23.5 ± 3.4	B[#]	0.09
Serum albumin (g/l)	35.9 ± 5.3	38.9 ± 4.5	34.4 ± 5.1	38.5 ± 2.3	35.2 ± 6.1	B[#]	0.04
Haemoglobin (g/dl)	11.6 ± 1.9	12.3 ± 1.2	11.1 ± 1.7	12.7 ± 2.3	11.2 ± 2.2	B[#]	0.01
Total cholesterol (mmol/l)	4.6 ± 1.1	5.1 ± 1.2	4.6 ± 1.1	4.1 ± 0.9	4.3 ± 1.0	A[#]	0.09
[c]Serum triglycerides (mmol/l)	1.39 (1.11-2.05)	1.14 (1.18-1.93)	1.29 (0.78-1.78)	1.78 (1.32-2.05)	1.28 (1.06-2.56)	NS	0.63
[c]CRP (mg/l)	6 (4-12.5)	4 (4-10)	6 (4-15)	6 (4-10)	6 (4-11)	NS	0.30

[a]n=69; [b]n=67; [c]Median (25-75th percentile); A refers to p-value for gender, B refers to p-value for mGFR<60 and AxB represents gender x mGFR interaction; [#]p<0.05; ˆp≤0.01; *p≤0.001; NS, no significant difference; BMI, body mass index; LBMI, lean BMI; FBMI, fat BMI; mGFR, measured glomerular filtration rate; CRP, C-reactive protein.

Table 2. Correlation coefficients between body composition parameters and other study variables

Parameter	Whole body lean mass	Trunk lean mass	Limb lean mass	Whole body fat mass	Whole body percent fat	Trunk fat mass	Trunk percent fat	Limb fat mass
Age (years)	0.028	0.040	0.021	0.291[b]	0.331[b]	0.323[b]	0.384[c]	0.241[a]
Body mass index (kg/m^2)	0.496[c]	0.402[c]	0.569[c]	0.931[c]	0.753[c]	0.899[c]	0.778[c]	0.885[c]
Waist-to-height ratio	0.363[c]	0.322[b]	0.389[c]	0.774[c]	0.692[c]	0.816[c]	0.757[c]	0.674[c]
Waist circumference (cm)	0.556[c]	0.518[c]	0.567[c]	0.771[c]	0.607[c]	0.837[c]	0.706[c]	0.646[c]
[d]mGFR ($ml/min/1.73m^2$)	0.159	0.124	0.177	0.225	0.171	0.230	0.182	0.200
Serum creatinine (µmol/l)	0.075	0.074	0.060	-0.275[a]	-0.295[b]	-0.268[a]	-0.276[a]	-0.265[a]
Urea (mmol/l)	0.010	0.027	-0.009	-0.229	-0.206	-0.234	-0.204	-0.210
Serum bicarbonate (mmol/l)	0.105	0.102	0.107	0.337[b]	0.328[b]	0.302[b]	0.311[b]	0.344[b]
Serum albumin (g/l)	0.301[b]	0.328[b]	0.261[a]	0.165	0.089	0.219	0.147	0.099
Haemoglobin (g/dl)	0.362[b]	0.384[c]	0.322[b]	0.233	0.192	0.320[b]	0.295[b]	0.133
Total cholesterol (mmol/l)	-0.259[a]	-0.265[a]	-0.221	-0.056	0.072	-0.074	0.044	-0.030
Log serum triglycerides	0.058	0.137	-0.009	-0.137	-0.156	-0.047	-0.085	-0.208
Log C-reactive protein	-0.006	-0.039	0.030	0.074	-0.041	0.087	0.001	0.059

[a]$p<0.05$; [b]$p\leq0.01$; [c]$p\leq0.001$; [d]$n=69$; mGFR, measured glomerular filtration rate.

Table 3. Univariate and multivariate regression analysis of factors associated with whole body lean mass

Variable	Females				Males			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	βeta coefficient	p-value	βeta coefficient	p-value	βeta coefficient	p-value	βeta coefficient	p-value
Age (years)	0.24	0.10			-0.25	0.26		
HIV (Yes/No)	-0.23	0.11			-0.50	**0.02**		
Serum bicarbonate (mmol/l)	0.17	0.25			0.13	0.56		
Serum albumin (g/l)	0.16	0.28			0.58	**0.006**		
Haemoglobin (g/dl)	0.14	0.34			0.63	**0.002**		
CRP (mg/l)	0.07	0.64			-0.24	0.29		
Total cholesterol (mmol/l)	-0.24	0.10			-0.10	0.67		
mGFR (ml/min/1.73 m^2)	0.08	0.59			0.54	**0.02**		
HIV (Yes/No)			-0.19	0.26			-0.17	0.46
Serum albumin (g/l)			0.05	0.77			0.43	**0.03**
Haemoglobin (g/dl)			0.03	0.85			0.23	0.22
GFR (ml/min/1.73 m^2)			0.03	0.87			0.33	0.10

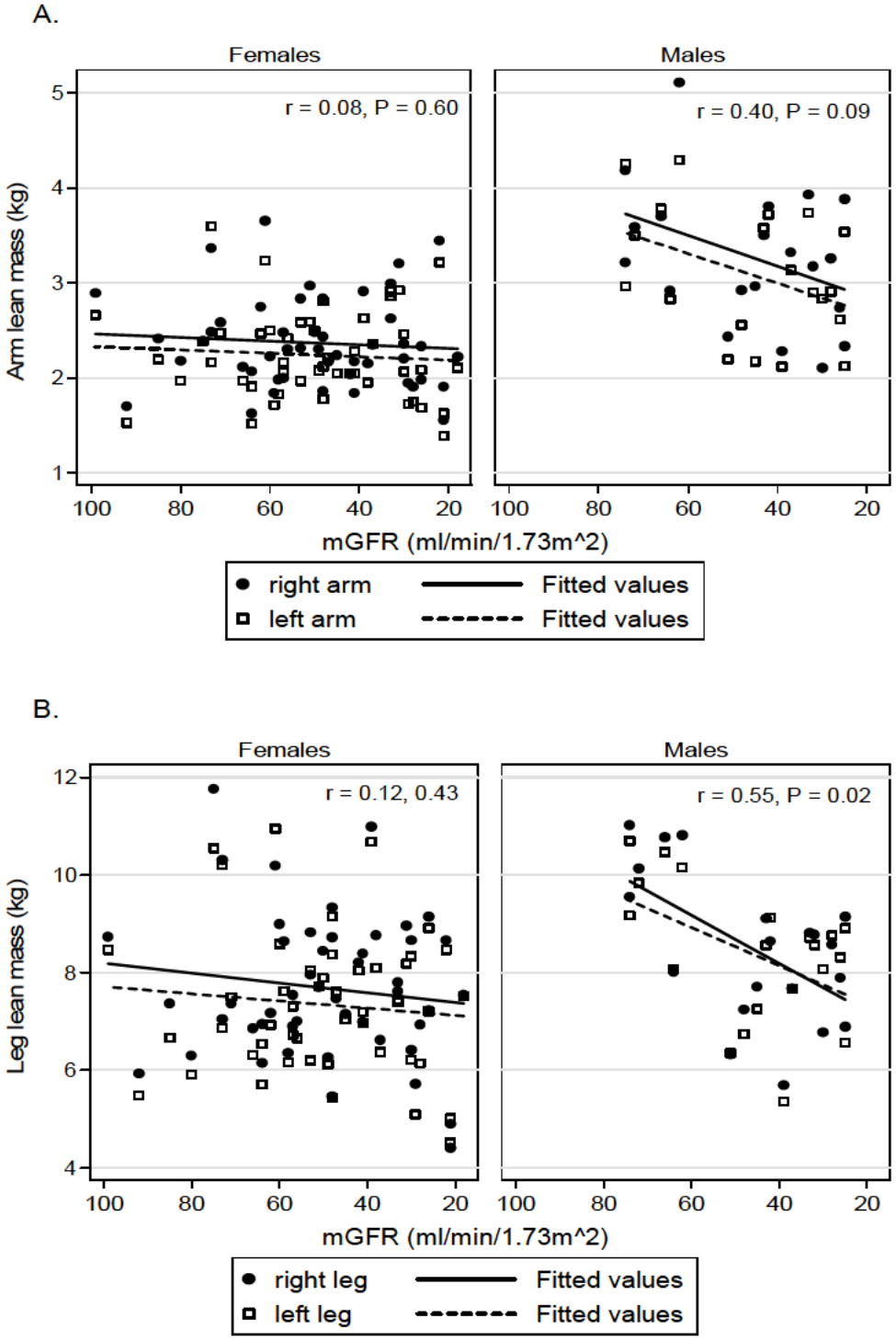
$R^2 = 0.06$, p=0.61 in females and $R^2 = 0.63$, p=0.005 in males; CRP, C-reactive protein; mGFR, measured glomerular filtration rate.

Table 4. Univariate and multivariate regression analysis of factors associated with whole body fat mass

Variable	Females				Males			
	Unadjusted		Adjusted		Unadjusted		Adjusted	
	βeta coefficient	P-value	βeta coefficient	P-value	βeta coefficient	P-value	βeta coefficient	P-value
Age (years)	0.38	**0.007**			0.07	0.77		
HIV (Yes/No)	-0.09	0.55			-0.61	**0.003**		
Serum bicarbonate (mmol/l)	0.32	**0.03**			0.42	0.05		
Serum albumin (g/l)	0.18	0.21			0.29	0.20		
Haemoglobin (g/dl)	0.19	0.20			0.57	**0.006**		
CRP (mg/l)	0.28	0.06			-0.17	0.50		
Total cholesterol (mmol/l)	-0.15	0.30			-0.18	0.43		
Triglycerides (mmol/l)	-0.15	0.31			-0.05	0.82		
GFR (ml/min/1.73 m^2)	0.12	0.40			0.57	**0.01**		
Age (years)			0.49	**0.005**			-0.23	0.47
HIV (Yes/No)			0.29	0.09			-0.25	0.37
Serum bicarbonate (mmol/l)			0.03	0.88			0.16	0.63
Haemoglobin (g/dl)			0.14	0.39			-0.22	0.49
CRP (mg/l)			0.29	0.05			0.02	0.92
GFR (ml/min/1.73 m^2)			0.18	0.28			0.63	**0.04**

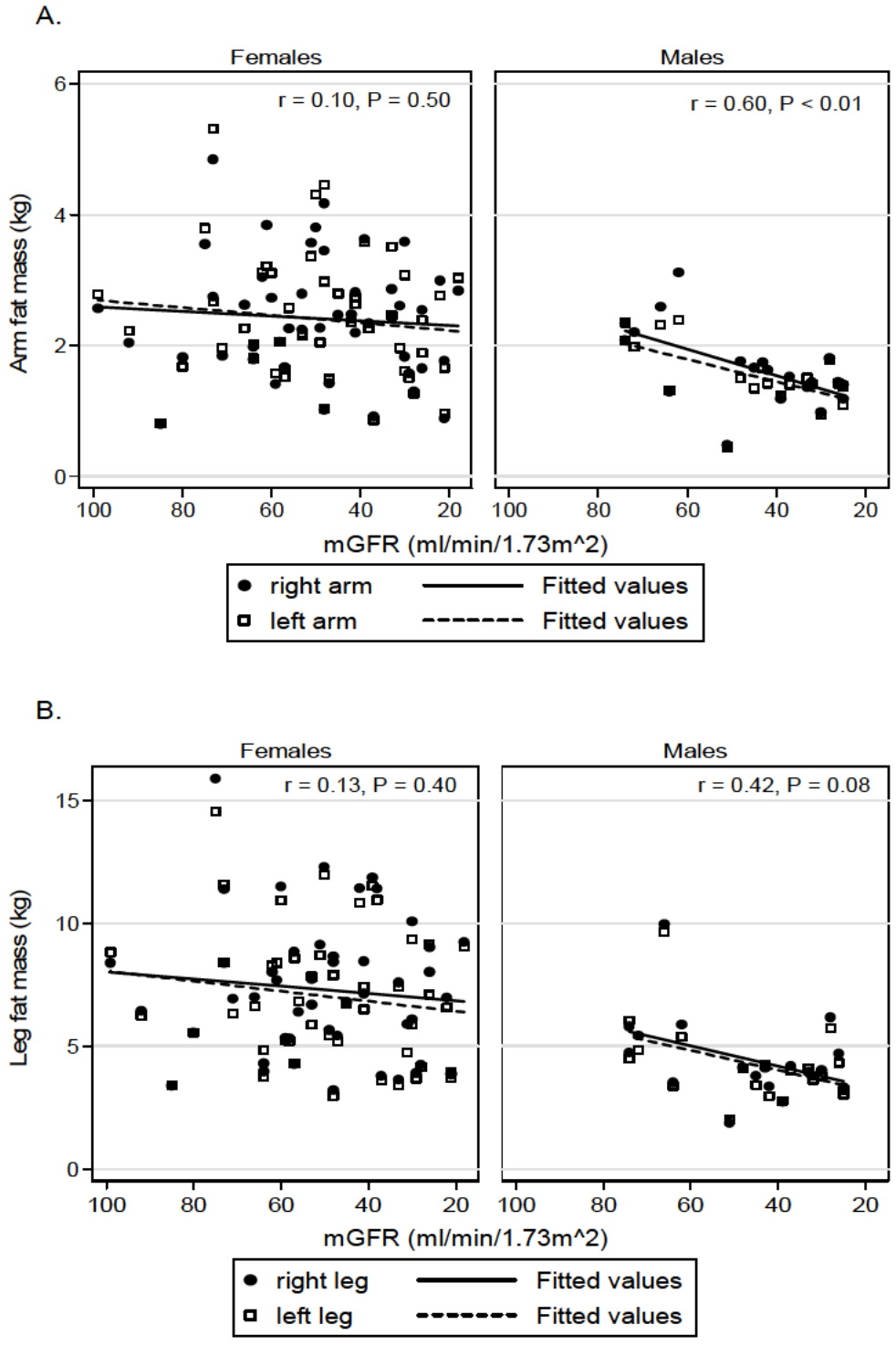
$R^2 = 0.30$, p=0.02 in females and $R^2 = 0.52$, p=0.16 in males; CRP, C-reactive protein; GFR, glomerular filtration rate.

Figure 1. Relationship between limb lean mass and measured glomerular filtration rate by gender.



A. There was no correlation between arm lean mass and mGFR in females while weak correlation was seen in males. **B.** Leg lean mass decreased significantly as mGFR declined in males (r=0.55, p=0.02) and not in females.

Figure 2. Relationship between limb fat mass and measured glomerular filtration rate by gender.



A. There was no correlation between arm fat mass and mGFR in females while arm fat mass decreased significantly with mGFR in males (r = 0.60, p=0.007) **B.** Weak correlation of leg fat mass with mGFR was seen in males and none in females.

CHAPTER 6

PREDICTIVE PERFORMANCE OF eGFR EQUATIONS IN SOUTH AFRICANS OF AFRICAN AND INDIAN ANCESTRY COMPARED WITH ^{99m}Tc-DTPA IMAGING

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NEPHROLOGY ORIGINAL PAPER

Predictive performance of eGFR equations in South Africans of African and Indian ancestry compared with ^{99m}Tc-DTPA imaging

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Abstract
Background South African guidelines for early detection and management of chronic kidney disease (CKD) recommend using the Cockcroft Gault (CG) or Modification of Diet in Renal Disease (MDRD) equations for calculating estimated glomerular filtration rate (eGFR) with the correction factor, 1.212, included for MDRD-eGFR in black patients. We compared eGFR against technetium-99m-diethylene-triaminepentaacetic acid (^{99m}Tc-DTPA) imaging.
Methods Using clinical records, we retrospectively recorded demographic, clinical, and laboratory data as well as ^{99m}Tc-DTPA-measured GFR (mGFR) results obtained from routine visits. Data from 148 patients of African ($n = 91$) and Indian ($n = 57$) ancestry were analyzed.
Results Median (IQR) mGFR was 38.5 (44) ml/min/1.73 m^2, with no statistical difference between African and Indian patients ($P = 0.573$). In African patients with stage 3 CKD, MDRD-eGFR (unadjusted for black ethnicity) overestimated mGFR by 5.3% [2.0 (16.0) ml/min/1.73 m^2] compared to CG-eGFR and MDRD-eGFR (corrected for black ethnicity) that overestimated mGFR by 17.7% [6.0 (15.0) ml/min/1.73 m^2] and 17.1% [6.0 (17.5) ml/min/1.73 m^2], respectively. In stage 1 2, CKD eGFR overestimated mGFR by 52.5, 38.0, and 19.3% for CG, MDRD (ethnicity-corrected), and MDRD (without correction), respectively. In Indian stage 3 CKD patients, MDRD-eGFR underestimated mGFR by 35.6% [−21.0 (6.5) ml/min/1.73 m^2] and CG-eGFR by 4.4% [−2.0 (27.0) ml/min/1.73 m^2], while in stage 1 2 CKD, CG-eGFR and MDRD-eGFR overestimated mGFR by 13.8 and 6.3%, respectively.
Conclusion MDRD-eGFR calculated without the African-American correction factor improved GFR prediction in African CKD patients and using the MDRD correction factor of 1.0 in Indian patients as in Caucasians may be inappropriate.

Keywords African · CKD · Cockcroft Gault · Glomerular filtration rate · Indian South Africans · MDRD

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Introduction

Strategies aimed at stemming the tide of CKD depend on its early detection, which requires that the GFR level can be easily determined with reasonable accuracy. Prediction equations provide a practical alternative method for estimating GFR in routine clinical practice to the costly gold standard methods for measuring GFR from clearance of exogenous markers such as inulin, technetium-99m-diethylene-triaminepentaacetic acid (^{99m}Tc-DTPA), and chromium-51-ethylenediaminetetraacetic acid (^{51}Cr-EDTA). The original 6-variable Modification of Diet in Renal Disease (MDRD) equation was shown to be highly accurate in predicting measured GFR in stable American CKD outpatients and the subsequent abbreviated 4-variable MDRD equation performed as well [1, 2]. The MDRD includes a correction factor of 1.212 for black ethnicity based on a 21% higher GFR in African-Americans than in whites [2]. The more recent Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was found to be more accurate than the MDRD [3].

The South African Renal Society CKD guidelines, adopted in 2006, recommend using the Cockcroft Gault (CG) or MDRD equations with inclusion of the correction factor 1.212 in black patients, while the correction factor is 1.0 for other ethnic groups [4]. This is based on the Kidney Dialysis Outcomes Initiative (K/DOQI) guidelines published in 2002 [5]. Few studies have evaluated the equations against the gold standard measured GFR methods in Africans. Furthermore, there are no validation studies in Indian South Africans. In the only published South African validation study that only included black patients, van Deventer et al. concluded that CG-eGFR and MDRD-eGFR, without correcting for black ethnicity, performed better than MDRD-eGFR including the black ethnicity factor in predicting ^{51}Cr-EDTA-GFR [6]. Subsequently, the MDRD and CKD-EPI equations both performed better in a Ghanaian population, when the African-American-derived ethnicity correction factors were omitted, evaluated against creatinine clearance, suggesting the need for a new equation for sub-Saharan Africans [7]. The aim of this study was to evaluate the performance of the MDRD in predicting GFR in a multiethnic group of South African CKD outpatients against radioisotope-measured GFR (mGFR).

Subjects and methods

Subjects

We conducted a retrospective study at the adult renal clinic at King Edward VIII Hospital, Durban. The clinic sees approximately 150 stable CKD outpatients annually and is one of the only three nephrologist-run CKD referral clinics in the public health sector in KwaZulu-Natal (KZN), the second most populous province in South Africa, with a population of about 10.5 million, 80% being black (African ancestry) and 9% of Indian ancestry [8]. Both ethnic groups constitute the main patient population at our clinic. We reviewed patient hospital records, which are kept in the renal clinic, with the approval of the University of KwaZulu-Natal Ethics Committee.

Inclusion criteria: Eligibility criteria were the following: all patients aged $\geq$ 16 years who had had a clinic visit during the period from January 2004 to December 2006 and in whom results for serum creatinine as well as for the routine annual radioisotope mGFR were available.

Exclusion criteria: Patients without radioisotope mGFR or blood results for that period and those who had unstable serum creatinine levels, e.g., from an intercurrent illness were excluded.

Data collection

We recorded demographic data (age, gender, and ethnic group), clinical data (CKD etiology, blood pressure, and anthropometry), and results of routine investigations. Investigations performed in the routine care at our clinic include blood tests for serum creatinine, urea, electrolytes, calcium, phosphate, and albumin, done 3- to 6-monthly and radioisotope mGFR, done annually. For measuring radioisotope GFR, patients receive an intravenous injection of 100 μCi of ^{99m}Tc-DTPA.

Estimation of GFR from serum creatinine-based prediction equations

The following equations were used to estimate GFR:

a. MDRD equation: $\text{GFR} = \mathbf{186} \times (S_{cr}/88.4)^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female}) \times (1.212 \text{ if black})$ [2]

The abbreviated 4-variable MDRD formula was used in its original form, as the serum creatinine assay was not validated against isotope dilution mass spectrometry (IDMS) and values were not recalibrated to be IDMS traceable.

b. CG equation: GFR = [(140-age) × weight × (0.85 if female)]/(72 × S_{cr}) [9]

Statistical analysis

We used the Shapiro Wilk test to test for normality in continuous data. Normally distributed data were expressed as mean ± standard deviation with the *t*-test employed to assess differences between the two ethnic groups. Non-normal data were described using median and interquartile (25th 75th) range with the Mann Whitney test used to compare the two groups. Categorical data were described as proportions, and the chi-square test was used to test significance. Performance of the formulae in predicting GFR was assessed by comparing eGFR against radioisotope mGFR. The difference between eGFR and mGFR was determined as the median difference (bias) (i.e., median difference = eGFR − mGFR) and percent difference (relative bias) calculated as [(absolute median difference/mGFR)] × 100. To assess the relationship between eGFR and mGFR, Spearman's rank correlation was calculated, and the Bland Altman method used to assess concordance between each eGFR equation and mGFR [10]. Accuracy was determined as the proportion of eGFR values that fell within 30% of mGFR (P_{30}) and those within 50% of mGFR (P_{50}). Stata10 software package was used.

Results

A total of 148 patients met the inclusion criteria, 91 (61.5%) of African ancestry and 57 (38.5%) of Indian ancestry. Mean age of the study population was 41.4 ± 13.1 years, and 62.8% of patients were women. The major causes of CKD were glomerulonephritis and hypertension, accounting for 39.2 and 34.4%, respectively. Other causes were tubulointerstitial nephritis (8.8%), diabetic nephropathy (7.4%), and autosomal dominant polycystic kidney disease (6.8%), and etiology was unknown in 3.4% of patients. None of the patients had human immunodeficiency virus (HIV) infection. Before the widespread government antiretroviral treatment program began in 2007, HIV-positive patients with CKD were often not followed up at our clinic as they were excluded from renal replacement therapy. Two-thirds of patients (100/148) had mGFR < 60 ml/min/1.73 m^2, in keeping with a prevalence of CKD stages 3 5 of 70.3% in African patients and 63.2% in Indian

Table 1 The demographic, clinical, and laboratory characteristics of the 148 patients studied

Parameter	African South Africans *n* 91	Indian South Africans *n* 57	*P* value
Age (years)	41.4 ± 13.1	41.5 ± 14.9	0.488
Systolic blood pressure (mmHg)	133.6 ± 20.2	130.1 ± 20.6	0.349
Diastolic blood pressure (mmHg)	79.5 ± 17.6	74.6 ± 14.4	0.084
Hemoglobin (g/dl)	12.1 ± 2.3	11.7 ± 2.0	0.267
Serum albumin (g/l)	32.5 ± 8.2	34.5 ± 8.6	0.164
Urea (mmol/l)[a]	9.8 (10.5)	9.1 (13.4)	0.634
Serum creatinine (μmol/l)[a]	155.5 (195)	187 (282)	0.257
Radioisotope mGFR (ml/min/1.73 m^2)[a]	37 (38)	41 (49)	0.573
CG eGFR (ml/min/1.73 m^2)[a, b]	45 (77)	40.5 (46)	0.052
MDRD eGFR with correction factor of 1.212 (ml/min/1.73 m^2)[a]	48 (58)	Not applicable	
MDRD eGFR without correction factor of 1.212 (ml/min/1.73 m^2)[a]	40 (48.5)	44.2 (60.7)	0.232

[a] Non normal data expressed as median (interquartile range)

[b] Weight unknown in 4 subjects, therefore, in calculating CG eGFR *n* 88 for African patients and *n* 56 for Indian patients

patients ($P = 0.36$). Overall median mGFR was 38.5 (44) ml/min/1.73 m^2. Demographic, clinical, and laboratory characteristics were similar in the two ethnic groups (Table 1). Body weight was not available in 4 patients; thus, CG-eGFR was calculated in only 88/91 (96.7%) African patients and 56/57 (98.2%) Indian patients.

Prediction equations showed a strong statistically significant linear relationship with mGFR in both groups. The Spearman correlation coefficient (r) values in the African group were 0.86, 0.86, and 0.87 for CG, MDRD with correction factor, and MDRD without correction factor, respectively. For the Indian group, the r values were 0.77 and 0.82 for CG and MDRD, respectively, without any ethnicity adjustment in calculating MDRD-eGFR. Bland Altman plots showed greater agreement between eGFR and mGFR when GFR was <60 ml/min/1.73 m^2 for all equations, while concordance was poorer at higher GFR levels (Fig. 1).

Table 2 shows eGFR performance in the African group. In patients with advanced CKD (stages 4 5 CKD or mGFR <30 ml/min/1.73 m^2), all 3 equations underestimated mGFR. CG-eGFR showed the best prediction with the smallest median difference of −1.0 (10.0) ml/min/1.73 m^2 (percent difference = 4.8%) as well as the highest P_{30} of 69.6% and P_{50} of 91.3%. In those with stage 3 CKD (mGFR 30 59 ml/min/1.73 m^2), the best estimate was observed when the MDRD was used without correcting for ethnicity, where eGFR overestimated mGFR by 2.0 (16.0) ml/min/1.73 m^2, (percent difference of 5.3%) with a P_{30} and P_{50} of 65.2 and 82.6%, respectively, while CG and MDRD adjusted for ethnicity overestimated mGFR to a greater degree. All equations overestimated mGFR when mGFR was ≥60 ml/min/1.73 m^2 (stages 1 2 CKD), with the best prediction observed when the MDRD equation was used without adjusting for black ethnicity (Table 2).

In Indian patients (Table 3), both CG and MDRD underestimated mGFR in those with CKD stages 3 5, with CG outperforming MDRD. In stage 4 5 CKD, CG-eGFR was 6.5 (11.3) ml/min/1.73 m^2 lower than mGFR (percent difference = 27%), while MDRD-eGFR was 12 (11.0) ml/min/1.73 m^2 or 46.2% lower than mGFR. Similarly, accuracy by P_{30} and P_{50} was much lower with MDRD than with CG. Performance was better in stage 3 CKD patients than in stages 4 5, with CG-eGFR being 4.4% lower than mGFR and MDRD-eGFR 35.5% lower. Both equations overestimated mGFR in patients with stages 1 2 CKD (Table 3).

Discussion

The CG and MDRD prediction equations are the recommended methods for estimating GFR in the South African CKD early detection and management guidelines, with the ethnicity factor of 1.212 included when using the MDRD equation in those of African ancestry (black South Africans), while it is omitted in other ethnic groups. However, validation studies are few in sub-Saharan Africa and the equations have not been validated in a multiethnic cohort of stable CKD outpatients in South Africa. Using ^{99m}Tc-DTPA mGFR as the gold standard, our data showed that CG and MDRD equations overestimated mGFR in black South Africans with CKD stages 1 3, and this was exaggerated threefold when the correction factor that was derived in African-Americans was included in the MDRD with MDRD-eGFR being 17.1 and 5.3% higher than mGFR in patients with stage 3 CKD with and without the correction factor, respectively. In stage 1 2 Indian patients, eGFR was also shown to overestimate mGFR. The study cited earlier that was performed in black African patients from a single center in Gauteng, one of the provinces of South Africa, did not include other ethnic groups. That study reported that the predictive performance of the 4-variable MDRD equation was better when the black ethnicity correction factor of 1.212 was omitted [6]. The authors cited their heterogeneous study population that included hospitalized patients, HIV-infected patients, and potential kidney donors as a limitation.

Our observations provide further evidence that the African-American-derived correction factor is not required in black South Africans. The need for a new equation that will be more suitable for the lean populations of sub-Saharan Africa was suggested in a recent publication from Ghana [7]. Eastwood et al. reported that in rural Ghanaians, the 4-variable MDRD as well as CKD Epidemiology Collaboration (CKD-EPI) equations overestimated 24-h creatinine clearance and CG-eGFR when the African-American-derived correction factors of 1.212 and 1.159 were included in the respective equations with improved accuracy when the ethnicity correction factors were omitted [7]. Filtration markers were not used, and

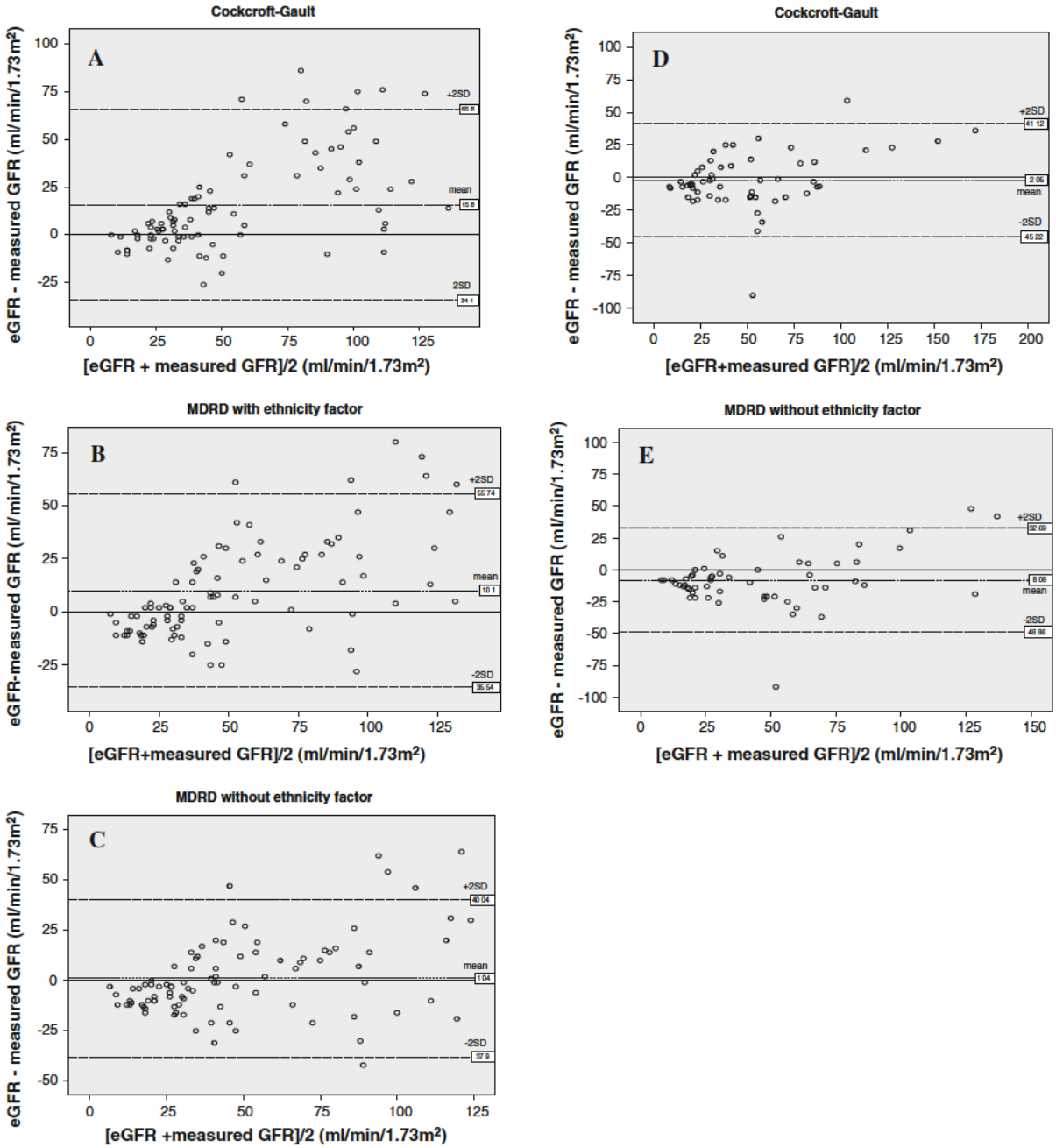

Fig. 1 Bland Altman plots illustrating concordance between ^{99m}Tc DTPA measured GFR (mGFR) and estimated GFR (eGFR), shown as mean difference (eGFR mGFR) plotted against the average of the 2 methods. A to C illustrates performance in African patients, and D to E shows performance in Indian patients. The dotted lines indicate mean difference; the dashed lines indicate upper and lower 95% confidence limits

over 85% of participants had normal kidney function with underrepresentation of CKD patients [7]. The median mGFR (IQR) in our study was 38.5 (44) ml/min/1.73 m^2. This was similar to the MDRD study population of stable CKD patients (mean GFR of 39.8 ± 21.2 ml/min/1.73 m^2) in which the equation was developed [1]. Serum creatinine-based prediction equations have been reported to be inaccurate at

Table 2 Performance of GFR prediction equations in 91 black South African CKD patients compared to ^{99m}Tc DTPA measured GFR

eGFR (ml/min/1.73 m^2)	*n*	Median ^{99m}Tc DTPA GFR (IQR) [ml/min/1.73 m^2]	Median difference (IQR) [ml/min/1.73 m^2]	Percent difference	P30%	P50%
CG[a]						
<30	23	21.0 (8.0)	1.0 (10.0)	4.8	69.6	91.3
30 59	31	34.0 (12.0)	6.0 (15.0)	17.7	56.7	77.7
≥60	34	71.5 (37.0)	37.5 (36.5)	52.5	35.3	47.1
MDRD with correction factor (1.212)						
<30	30	24.0 (10.5)	7.0 (9.0)	29.2	53.3	86.7
30 59	24	35.5 (18.3)	6.0 (17.5)	17.1	62.5	79.2
≥60	37	71.0 (36)	27.0 (28.0)	38.0	35.1	62.2
MDRD without correction factor (1.212)						
<30	36	25.5 (15.0)	10.0 (9.0)	39.2	36.1	66.7
30 59	23	38.0 (19.0)	2.0 (16.0)	5.3	65.2	82.6
≥60	32	72.5 (36.3)	14.0 (36.3)	19.3	68.8	78.1

[a] Weight unknown in 3 subjects, therefore, *n* 88 for CG eGFR

Table 3 Performance of GFR prediction equations in 57 Indian South African CKD patients compared to ^{99m}Tc DTPA measured GFR

eGFR (ml/min/1.73 m^2)	*n*	Median ^{99m}Tc DTPA GFR (IQR) [ml/min/1.73 m^2]	Median difference (IQR) [ml/min/1.73 m^2]	Percent difference	P30%	P50%
CG[a]						
<30	20	24.0 (9.8)	6.5 (11.3)	27.0	45.0	70.0
30 60	21	45.0 (30.5)	2.0 (27.0)	4.4	52.4	76.2
≥60	15	87.0 (30)	12.0 (34.6)	13.8	80.0	86.7
MDRD without correction factor						
<30	27	26.0 (11.0)	12.0 (11.0)	46.2	29.6	48.1
30 60	13	59.0 (31.0)	21.0 (6.5)	35.6	23.1	92.3
≥60	17	80.0 (27.5)	5.0 (12.5)	6.3	76.5	94.1

[a] Weight unknown in 1 subject, therefore, *n* 56 for CG eGFR

higher GFR levels as shown in healthy potential kidney donors [11 15]. Consequently, current recommendations are to report eGFR as ≥60 ml/min/1.73 m^2 for values above 60 ml/min/1.73 m^2 and only report the specific value when eGFR is <60 ml/min/1.73 m^2 [16]. Therefore, it is not surprising that in African patients in our study agreement between eGFR and mGFR was poorer when mGFR was ≥60 ml/min/1.73 m^2. The findings in Indian patients were contrary, in that agreement tended to be better in those with stages 1 2 CKD compared to stages 3 5.

Lower accuracy for eGFR equations has also been reported in patients with advanced CKD (stages 4 5) as well as variable performance according to GFR level within the same population [17, 18]. In ESRD patients, MDRD-eGFR underestimated mGFR by inulin clearance (C_{in}) when C_{in} was >8 ml/min/1.73 m^2 but overestimated it when C_{in} was <8 ml/min/1.73 m^2 [18]. A more recent multi-center study of 2208 subjects reported better accuracy for CG-eGFR and MDRD-eGFR compared with C_{in} at higher GFR levels with a decline in accuracy with each consecutive lower mGFR group [19]. In that study, P_{30} for mGFR < 60 ml/min/1.73 m^2 was 59.1% for CG and 63.2% for MDRD, while the proportions for both equations were higher at 78.8 and 72.9%, respectively, at mGFR levels ≥60 ml/min/.73 m^2. In the subgroups with advanced CKD (stages 4 and

5), accuracy was much lower at 31.5 54.9 and 40.8 56.0% for CG and MDRD, respectively, being lowest in stage 5 patients [19]. This trend was observed in the patients of Indian ancestry in our study. The poorer performance and low accuracy of eGFR at advanced CKD stages was also evident in our Indian patients with both CG-eGFR and MDRD-eGFR underestimating mGFR ($P_{30} = 45\%$ for CG and 29.6% for MDRD). Similarly, MDRD-eGFR performed poorly in those of African ancestry; however, CG-eGFR, while it still underestimated mGFR, surprisingly showed better predictive performance in advanced than in earlier CKD patients from this ethnic group. The relatively better performance by CG may be because CG-eGFR underestimated mGFR to a lesser degree than MDRD, since it measures creatinine clearance, which overestimates mGFR [9].

The underestimation of mGFR by eGFR in advanced (stages 4 5) CKD patients in our study suggests that serum creatinine levels may be disproportionately higher than expected for a given mGFR level, thus raising speculation of increased muscle catabolism in this group. Muscle catabolism has been well documented as a frequent complication in uraemic patients for over 40 years [20, 21]. More recent studies have shown that low protein intake and metabolic acidosis worsen this muscle protein loss [22]. These factors were not evaluated in our study.

This is the first study to evaluate the performance of eGFR equations in Indian South African patients. Studies in different Asian populations have shown poor predictive performance of various eGFR equations, including the MDRD equation, when evaluated against mGFR [15, 23 25]. MDRD-eGFR was reported to underestimate mGFR in the Chinese population, while it overestimated mGFR in Japanese patients, and performance significantly improved with addition of a coefficient derived specifically for each ethnic group resulting in lower bias, as well as higher accuracy (P_{30} values $> 70\%$) [25, 26]. CG and MDRD equations overestimated 24-h creatinine clearance in South Asians from Pakistan, with a tendency toward greater overestimation by the MDRD [24].

The reported ethnic differences in predictive performance of eGFR equations illustrate a major limitation of serum creatinine-based eGFR equations because factors other than GFR affect serum creatinine levels such as muscle mass and dietary protein. Creatinine generation has been shown to be low in people with low muscle mass and those on low-protein diets, resulting in serum creatinine levels that are lower than expected for a given GFR level [27]. Muscle mass may be lower in black South Africans as their ancestry differs from that of African-Americans. Dietary protein intake has been reported to be lower in black South Africans compared to their white counterparts and African-Americans [28, 29]. Thus, we speculate that in early CKD creatinine generation may be low, resulting in low serum creatinine levels and spuriously higher eGFR levels, overestimating mGFR. The overestimation is further exaggerated when the ethnicity correction factor of 1.212 is included, as it adjusts for a higher GFR in African-Americans. We propose the same explanation for the overestimation observed in Indian South Africans with stage 1 2 CKD as well, since their muscle mass may also be lower than in the populations used in developing the eGFR equations and vegetarian diets are likely to be more prevalent in this ethnic group. Performance of CG and MDRD equations has also been evaluated by assessing the proportion of patients correctly classified into their "true" measured GFR category. Proportions correctly classified vary with each equation and in the different CKD stages, with misclassification reported in 30 50% of patients [19]. We did not measure this in our study; however, it is likely that the different subject numbers observed for each GFR subgroup with each equation were due to differences in classification of patients into their mGFR group.

This study provides further evidence to the two previously cited reports from sub-Saharan Africa [6, 7] that the current practice of including the African-American correction factor in Africans is not justified. Furthermore, using the MDRD unadjusted as in Caucasians in Indian patients may also be inappropriate. The strength of the study is that stable CKD outpatients were studied; thus, their creatinine generation was presumably stable. Selection bias may have occurred with inclusion of only patients with available mGFR results, but we expect this to be minimal since mGFR is available and often routinely performed annually in the follow-up care in our clinic. The study limitations are (i) The small sample size; (ii) IDMS was not used and serum creatinine levels were not re-calibrated and standardized to MDRD values; (iii) The fact that we included patients

seen over a 2-year period could have resulted in bias from undetected serum creatinine assay drift over time; (iv) The potential for selection bias still exists as the study was retrospective and the CKD population followed up at our clinic was highly selected, as seen with exclusion of HIV-infected patients at that time, which fortunately no longer applies; (v) Misclassification bias may have occurred between the eGFR equations.

Our results underscore the importance of validation studies prior to implementing measurement tools developed in different populations and provide further evidence that an alternative equation is required for Africans. A prospective design is required to investigate the relationship between muscle catabolism, creatinine generation as well as their effect on GFR estimation in our population. In the meantime, we suggest using the MDRD omitting the African-American correction factor in black South Africans until further evaluation data including the CKD-EPI equation become available. Furthermore, we suggest for the first time that using the current MDRD in South Africans of Indian ancestry may not be appropriate and that a correction factor or a new equation is needed to improve prediction in this ethnic group as well.

References

1. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D (1999) A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation for the Modification of Diet in Renal Disease Study Group. Ann Intern Med 130:461 470
2. Levey AS, Greene T, Kusek J et al (2000) A simplified equation to predict glomerular filtration rate from serum creatinine (abstract). J Am Soc Nephrol 11:155A
3. Levey AS, Stevens LA, Schmid CH (2009) A new equation to estimate glomerular filtration rate. Ann Intern Med 150:604 612
4. South African Renal Society recommendations for Early Detection and Management of Chronic Kidney Disease. www.sa renalsociety.org (accessed 12th November 2009)
5. National Kidney Foundation K/DOQI (2002) Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis 39:S1 S266
6. van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ (2008) Estimating glomerular filtration rate in black South Africans by use of the modification of diet in renal disease and Cockcroft Gault equations. Clin Chem 54: 1197 1202
7. Eastwood JB, Kerry SM, Plange Rhule J et al (2010) Assessment of GFR by four methods in adults in Ashanti, Ghana: the need for an eGFR equation for lean African populations. Nephrol Dial Transpl 25:2178 2187
8. Mid year 2009 population estimates. www.statssa.gov.za (accessed 17th November 2009)
9. Cockcroft DW, Gault MH (1976) Prediction of creatinine clearance from serum creatinine. Nephron 16:31 41
10. Bland JM, Altman DG (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1:307 310
11. Rule AD, Gussak HM, Pond GR et al (2004) Measured and estimated GFR in healthy potential kidney donors. Am J Kidney Dis 43:112 119
12. Rule AD, Larson TS, Bergstralh EJ, Slezak JM, Jacobsen SJ, Cosio FG (2004) Using serum creatinine to estimate glomerular filtration rate: accuracy in good health and in chronic kidney disease. Ann Intern Med 141:929 937
13. Bostom AG, Kronenberg F, Ritz E (2002) Predictive per formance of renal function equations for patients with chronic kidney disease and normal serum creatinine levels. J Am Soc Nephrol 13:2140 2144
14. Poggio ED, Wang X, Greene T et al (2005) Performance of the Modification of Diet in Renal Disease and Cockcroft Gault equations in the estimation of GFR in health and in chronic kidney disease. J Am Soc Nephrol 16:459 466
15. Mahajan S, Mukhiya GK, Singh R et al (2005) Assessing glomerular filtration rate in healthy Indian adults: a com parison of various prediction equations. J Nephrol 18: 257 261
16. Myers GL, Miller WG, Coresh J et al (2006) Recom mendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem 52:5 18
17. Hallan S, Asberg A, Lindberg M, Johnsen H (2004) Val idation of the Modification of Diet in Renal Disease for mula for estimating GFR with special emphasis on calibration of the serum creatinine assay. Am J Kidney Dis 44:84 93
18. Kuan Y, Hossain M, Surman J, El Nahas AM, Haylor J (2005) GFR prediction using the MDRD and Cockcroft and Gault equations in patients with end stage renal dis ease. Nephrol Dial Transpl 20:2394 2401
19. Botev R, Mallié JP, Couchoud C (2009) Estimating glo merular filtration rate: Cockcroft Gault and Modification of Diet in Renal Disease formulas compared to renal inulin clearance. Clin J Am Soc Nephrol 4:899 906
20. Comty CM (1968) A longitudinal study of body compo sition in terminal uremics treated by regular hemodialysis. I. Body composition before treatment. Can Med Assoc J 98:482 491
21. Coles GA (1972) Body composition in chronic renal fail ure. Q J Med 41:25 47
22. Mitch WE, May RC, Maroni BJ (1989) Review: mecha nisms for abnormal protein metabolism in uremia. J Am Coll Nutr 8:305 309
23. Zuo L, Ma YC, Zhou YH, Wang M, Xu GB, Wang HY (2005) Application of GFR estimating equations in Chi nese patients with chronic kidney disease. Am J Kidney Dis 45:463 472

24. Jafar TH, Schmid CH, Levey AS (2005) Serum creatinine as marker of kidney function in South Asians: a study of reduced GFR in adults in Pakistan. J Am Soc Nephrol 16:1413 1419
25. Imai E, Horio M, Nitta K et al (2007) Estimation of glo merular filtration rate by the MDRD study equation mod ified for Japanese patients with chronic kidney disease. Clin Exp Nephrol 11:41 50
26. Ma YC, Zuo L, Chen JH et al (2006) Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 17:2937 2944
27. Manjunath G, Sarnak MJ, Levey AS (2001) Estimating the glomerular filtration rate: do's and don'ts for assessing kidney function. Postgrad Med 110:55 62
28. O'Keefe SJ, Kidd M, Espitalier Noel G, Owira P (1999) Rarity of colon cancer in Africans is associated with low animal product consumption, not fiber. Am J Gastroenterol 94:1373 1380
29. O'Keefe SJ, Chung D, Mahmoud N et al (2007) Why do African Americans get more colon cancer than Native Africans? J Nutr 137:175S 182S

CHAPTER 7

A GLOMERULAR FILTRATION RATE PREDICTION EQUATION DEVELOPED IN AFRICAN PATIENTS IN DURBAN, SOUTH AFRICA

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and

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Title: A glomerular filtration rate prediction equation developed in African patients in Durban, South Africa

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Abstract

Background

Existing serum creatinine-based estimated glomerular filtration rate (eGFR) equations are inaccurate in sub-Saharan Africans. African-American derived black ethnicity coefficients in currently-used eGFR equations result in GFR overestimation. The objective of this study was to develop a GFR estimating equation in Africans by modifying the Modification of Diet in Renal Disease (MDRD) equation to improve GFR prediction.

Methods

We enrolled 76 adult black African chronic kidney disease (CKD) patients. Technicium-99-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA) clearance was used as the gold standard GFR method. GFR prediction equations were developed from multivariable linear regression analysis models using the whole dataset for training and testing. Variables used in the 6-variable MDRD equation were modelled, namely age, gender, serum creatinine, urea, albumin, except ethnicity. Bias, precision and accuracy were calculated to evaluate concordance between ^{99m}Tc-DTPA-GFR and eGFR.

Results

Mean ^{99m}Tc-DTPA-GFR was 51.3 ± 22.6 ml/min/1.73m^2 and 89.6% had CKD. The modified MDRD equation for Africans showed the best GFR prediction, with the lowest bias (95% CI) of -0.72 (-5.17, 3.73) ml/min/1.73m^2 and root mean square error, 13.4 ml/min/1.73m^2 as well as highest accuracy within 30% of measured GFR of 75%. MDRD-eGFR performance was 6.21 (2.75, 9.67) ml/min/1.73m^2, 18.1 ml/min/1.73m^2 and 51.3% and by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) eGFR, 3.56 (0.27, 6.82) ml/min/1.73m^2, 17.1 ml/min/1.73m^2 and 63.2% for bias, RMSE and accuracy, respectively.

Conclusion

GFR prediction was improved by using an equation developed in Africans. An African modified equation may overcome the inaccuracy experienced with MDRD-eGFR and CKD-EPI eGFR.

Background

Serum creatinine remains the most widely used marker to estimate kidney function in clinical practice in CKD monitoring and remission programs. Methods considered as the gold standard for measuring GFR include clearance of exogenous markers such as inulin, technicium-99m-diethylenetriaminepentaacetic acid (^{99m}Tc-DTPA), chromium-51-ethylenediaminetetraacetic acid (^{51}Cr-EDTA), iodine-125-iothalamate (^{125}I-iothalamate) and iohexol; however, their use in routine patient care is not practical. Thus, Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend using a serum creatinine-based prediction equation for the initial assessment of glomerular filtration rate (GFR) and a further confirmatory test like cystatin C or a clearance method when estimated GFR (eGFR) is less accurate (1). Commonly used serum creatinine-based GFR prediction equations are: Cockcroft-Gault (CG), Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations as shown in Table 1 (2-4). The CG equation was developed in European patients while the MDRD and CKD-EPI equations were developed in Americans.

Validation studies have shown these equations to be inaccurate in predicting kidney function in Africans. All 3 equations showed poor performance in predicting GFR in a study of black South Africans in Gauteng province compared to ^{51}Cr-EDTA-GFR (5, 6). Similarly, poor predictive performance was reported in a Ghanaian community where both MDRD and CKD-EPI equations overestimated 24-hour creatinine clearance (7). Similar findings were reported in a study at our institution where MDRD-eGFR performance was evaluated against ^{99m}Tc-DTPA (8). Low accuracy of eGFR equations and their overall poor performance was also reported in various Asian populations while predictive performance was improved when a modified coefficient was included, which was specifically derived in each of these populations (9-13). Measures that are commonly used in most validation studies to evaluate the predictive performance of eGFR equations have included bias, defined as the average difference between eGFR and mGFR, root mean square error (RMSE) defined as the standard deviation of the differences, as well as accuracy within 30% (P_{30}), which is the percentage of GFR estimates within 30% of mGFR (14, 15). The study aim was to develop a GFR prediction equation in South Africans of African ancestry by modifying a currently used serum creatinine-based prediction equation.

Methods

Study setting and population

Participants in this cross-sectional study were recruited from participants in a screening study for CKD and associated complications at the King Edward VIII Hospital General Internal Medicine outpatients' clinic, which provides care to adults with various chronic diseases including those known to be associated with CKD, such as hypertension, diabetes, atherosclerotic cardiovascular disease (CVD) and HIV. Data collected included age, gender, height, weight, blood investigations for serum creatinine, urea and albumin as well as urine albumin: creatinine ratio. Patients found to have CKD based on MDRD-eGFR <60 ml/min/1.73m^2 and/or albuminuria ≥3 mg/mmol, according to KDIGO guidelines (1), were eligible to participate in this sub-study and were included if aged ≥18 years and of African ethnicity, following informed consent. Exclusion criteria were patients with: age <18 years old, acute intercurrent illness, acute kidney injury, use of drugs like trimethoprim and cimetidine, pregnancy as well as those who could not undergo ^{99m}Tc-DTPA measured GFR (mGFR). All tests were performed at King Edward VIII hospital laboratory, which is part of the National Health Laboratory Services (NHLS) in South Africa. Serum creatinine was measured using the isotope dilution mass spectrometry (IDMS)-traceable alkaline picrate assay (Roche Diagnostics, Germany) adopted by the NHLS in line with global recommendations to improve the accuracy of serum creatinine measurements (16).

Measurement of renal function

Radioisotope GFR measurement was performed according to a standard protocol routinely used in the Medical Physics Unit of the Radiology Department - at the same hospital. Briefly, an intravenous injection of 100μCi of ^{99m}Tc-DTPA was administered to well hydrated subjects. Subsequently, subjects underwent dual plasma sampling, with heparinized venous blood taken at 90 and 180 minutes. Radioactivity counts in the plasma were used to calculate GFR and results were normalized to body surface area. Existing serum creatinine based equations were used to calculate eGFR, namely CG, MDRD as well as CKD-EPI equations. The African American ethnicity coefficient was omitted in the latter two thus implying the ethnicity factor of 1.0. The CG equation was adjusted to body surface area (BSA) using the formula: CG x 1.73m^2/BSA.

Statistical analysis

Descriptive analysis

Univariate analysis was performed to describe the data and the Shapiro-Wilk test used to test numerical data for normality. Categorical data was described as proportions and numerical data summarized using mean ± standard deviation (SD) or median (interquartile range) (IQR) for non-normal data. To evaluate differences between groups, the chi-square test was used for categorical variables and t-test used for numerical data or Mann-Whitney test, when appropriate.

Multivariable regression analysis

Multiple linear regression analysis was performed. Variables included in the model were: age, gender as well as log-transformed values of serum creatinine, urea and albumin, which were re-transformed back to their original units in the multiplicative model for the final equation, using the approach by Levey et al. in the development of the original MDRD equation (17). We excluded ethnicity as a variable, as the study was performed on a homogenous ethnic sample. Training and testing were done in the same dataset as was undertaken in other studies (2, 17-19). Three phases of regression modelling were performed using five of the variables that were included in the original 6-variable MDRD equation. In the first phase, training was done using the whole dataset to produce the prediction equation (equation 1), which was tested on the whole study dataset then further testing done on male and female subsets separately. In the second phase, the dataset was divided into male and female subsets with training carried out separately in each subset to produce two further equations. The regression equation developed using the male subset as the training set (equation 2) was tested using the female subset as the test set and also tested using the whole dataset. A third equation was developed using females as the training subset and tested on the male subset as well as on the whole dataset (equation 3). In the third phase, the equation 1 from the first phase and equations 2 and 3 from the second phase were tested on the whole dataset to optimize the final prediction equation.

Assessment of the relationship as well as concordance between mGFR and eGFR

Correlation between mGFR and eGFR was assessed. To evaluate agreement between each eGFR equation and mGFR, we used the Bland Altman method, which regress the difference between eGFR and mGFR against the average of the two (20). The measures of concordance calculated were bias, RMSE and P_{30}. Precision was expressed as RMSE and the width of the 95% confidence limits of agreement was also documented. Statistical analysis was performed using

Intercooled Stata version 11 (Texas, USA) software. MATLAB R2014b Statistics Toolbox (MathWorks, USA) was used for developing the GFR prediction equation.

Results

Patient characteristics

Of 104 eligible patients, 76 black African participants were enrolled and 53 (69.7%) were female. Sixty-eight (89.6%) patients had mGFR <60 ml/min/1.73 m^2. Mean ^{99m}Tc-DTPA mGFR was 51.3 ± 22.6 ml/min/1.73m^2. Hypertension was present in 89.6%, diabetes mellitus in 35.1%, glomerulonephritis (HIV-negative) in 14.3%, HIV (13%) and tubulointerstitial diseases in 2.6%. Table 3 shows patient clinical and laboratory data as well as distribution by gender. As expected, serum creatinine levels were higher in males than females, however GFR levels were similar between the two genders. Almost 59% (31/53) of females were obese using the WHO BMI cut-off of >30 kg/m^2 compared with 17.4% (4/23) of males while 12/53 (22.6%) females and 14/23 (60.9%) males were overweight (p = 0.002). There were no other gender differences observed.

Modification of the MDRD equation for African populations

Equations 1, 2 and 3 obtained during the 3-phase development stage are shown in Table 3. The best prediction was obtained when the whole dataset (n = 76) was used for training (equation 1). To further improve the equation, the constant was adjusted while a coefficient for female gender was included. Thus, the final modified MDRD equation for Africans obtained is as follows:
African modified MDRD-eGFR =
$94.6324 \times \text{serum creatinine}^{-0.2814} \times \text{age}^{-0.2929} \times \text{urea}^{-0.2908} \times \text{albumin}^{0.4845}$ (x 0.9512 if female)

Predictive performance of the modified equation and comparison with existing equations

Using the African modified equation, mean eGFR was 52.0 ± 17.1 ml/min/1.73 m^2. Figure 1 shows good correlation of eGFR with mGFR for all equations (correlation coefficient, r = 0.7 to 0.81). Analysis of concordance between eGFR and mGFR showed that the African modified MDRD equation had the lowest bias (relative bias of 1.4%), RMSE, 95% limits of agreement and highest P_{30} accuracy of all the equations (Table 4, Figure 2). The lowest performance occurred with CG; although this improved when CG was adjusted for body surface area, it remained poor. CG_BSA, MDRD and CKD-EPI equations, all underestimated mGFR at lower GFR levels while they overestimated mGFR at higher levels (Table 5).

Discussion

Using data from African CKD patients, we developed a serum creatinine-based eGFR equation for Africans by modifying the original MDRD equation. The African modified equation showed the lowest bias, best precision, highest accuracy and correlation against ^{99m}Tc-DTPA mGFR of all equations evaluated in this patient cohort. Our proposed equation provides a significant step in addressing the need for a more accurate GFR-prediction equation for use in Africans. By using demographic variables (age and gender) as well as readily available biochemical markers, the equation offers a potential alternative to the currently used CG, MDRD and CKD-EPI equations that have been shown to be inaccurate in African populations (5-8, 21). Our earlier observation that MDRD-eGFR underestimated GFR at lower levels and overestimated it at higher levels was again confirmed (8), while a similar trend occurred with CKD-EPI eGFR in the present study.

Urea and albumin were included as in the original 6-variable MDRD equation although these were later omitted in the simplified abbreviated MDRD, after it was shown to perform as well as the original equation (3, 17). In developing the MDRD equation, the best performance was observed when demographic variables (age and gender), serum variables (creatinine and urea) plus urine urea nitrogen were included, however serum albumin was used to substitute urine urea nitrogen in the final 6-variable MDRD equation (17). Both urea and albumin are influenced by dietary protein, which was not measured in this study. Dietary protein intake was previously reported to be lower in black South Africans compared to African-Americans (22), and thus is likely to be lower in our study population than in the MDRD population. Dietary protein is known to modulate renal function and should be assessed in defining the normal renal function range in populations as differences in protein intake may account for differences in GFR (23, 24). Serum albumin was also included and considered a proxy for nutritional status (25). The prevalence of malnutrition was found to be high in our institution in previous studies of ESRD patients (26). While other markers of nutritional status were not analysed in the present study, mean serum albumin was low (normal range 35 – 42 g/l).

We encountered only one other published eGFR equation developed in Africans, which used data from black South African patients, n = 50 in the training dataset and n = 50 for validation against ^{51}Cr-EDTA-GFR (6). GFR prediction by the serum creatinine-based equation developed

in that study was comparable with the abbreviated MDRD and CKD-EPI equations (black ethnicity coefficients excluded in both) when GFR was <60 ml/min/1.73 m^2 while a serum cystatin C-based equation was shown to be more precise with mGFR ≥60 ml/min/1.73 m^2 (6). Comparison between the two studies is not possible due to differences in the methods used such as the GFR clearance methods and study subjects (<50% of patients had mGFR <60 ml/min/1.73 m^2 vs almost 90% in the present study).

An unexpected finding in developing the equation was the female coefficient of 0.9512. The female coefficient in existing GFR equations is 15% to 25% lower than in males, in the case of CG (2) and MDRD (17), respectively, reflecting lower muscle mass in females. A potential reason for the higher female coefficient (~5% lower than males) observed in our study, is the substantially high proportion of overweight and obese patients (>80% of females). This is in keeping with the high prevalence, especially in women, of overweight/obesity of 70% to 90% reported in some studies from our province of KwaZulu-Natal (27, 28). Extremes of body size, including obesity as well as malnutrition are among the well-documented sources of error encountered when using serum creatinine to estimate GFR, along with extremes of muscle mass, muscle wasting, dietary protein and other non-GFR determinants of serum creatinine (1). The influence of these factors on the final equation is unclear in the present study.

The main strengths in this study include the use of the clearance of an exogenous substance as a reference GFR method. Although inulin clearance is the gold standard for GFR measurement, ^{99m}Tc-DTPA is a well-established alternative. The use of the same laboratory, medical physics unit and clinical staff for all participants minimized observer as well as information bias, which is another strength. The major limitation is the small sample size used for equation development and testing. A large-scale study with participating centres is needed to further improve the proposed modified MDRD equation. The selection of patients with CKD is a source of bias as the equation is likely to perform differently in those with higher GFR levels or normal kidney function. Future studies that include normal individuals would ensure better prediction across the full range of GFR levels. Notwithstanding these limitations, we conclude that our results suggest that GFR prediction from serum creatinine could be improved in African CKD (≥G3) patients beyond the performance obtained from existing equations while maintaining low costs. More

efforts are needed to develop a more accurate prediction equation in Africans. Improved eGFR accuracy in the face of the growing obesity epidemic will likely prove challenging but is critical in kidney function evaluation and monitoring in under-resourced settings because of the limited availability of GFR confirmatory tests.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

Ethical standards

The study was approved by the University of KwaZulu-Natal Biomedical Ethics Committee. All participants gave written informed consent prior to their inclusion in the study

References

1. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO Clinical Practice Guideline for the Evaluation and Management of chronic kidney disease. Kidney Int Suppl. 2012;3(1):1-150.

2. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.

3. Levey AS, Greene T, Kusek J, *et al*. A simplified equation to predict glomerular filtration rate from serum creatinine (abstract). J Am Soc Nephrol. 2000;11:155A.

4. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

5. Van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ. Estimating glomerular filtration rate in black South Africans by use of the Modification of Diet in Renal Disease and Cockcroft-Gault equations. Clin Chem. 2008;54(7):1197-202.

6. van Deventer HE, Paiker JE, Katz IJ, George JA. A comparison of cystatin C- and creatinine-based prediction equations for the estimation of glomerular filtration rate in black South Africans. Nephrol Dial Transplant. 2011;26(5):1553-8.

7. Eastwood JB, Kerry SM, Plange-Rhule J, *et al*. Assessment of GFR by four methods in adults in Ashanti, Ghana: the need for an eGFR equation for lean African populations. Nephrol Dial Transplant. 2010:1-10.

8. Madala ND, Nkwanyana N, Dubula T, Naiker IP. Predictive performance of eGFR equations in South Africans of African and Indian ancestry compared with (99m)Tc-DTPA imaging. Int Urol Nephrol. 2012;44(3):847-55.

9. Ma YC, Zuo L, Chen JH, *et al*. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006;17(10):2937-44.

10. Imai E, Horio M, Nitta K, *et al*. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol. 2007;11(1):41-50.

11. Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis. 2010;56(1):32-8.

12. Chen LI, Guh JY, Wu KD, Chen YM, Kuo MC, Hwang SJ, et al. Modification of diet in renal disease (MDRD) study and CKD epidemiology collaboration (CKD-EPI) equations for Taiwanese adults. PLoS One. 2014;9(6):e99645.

13. Jeong TD, Lee W, Yun YM, Chun S, Song J, Min WK. Development and validation of the Korean version of CKD-EPI equation to estimate glomerular filtration rate. Clin Biochem. 2016;49(9):713-9.

14. Coresh J, Stevens L. Kidney function estimating equations: where do we stand? Curr Opin Nephrol Hypertens. 2006;15:276-84.

15. Rule AD. Understanding estimated glomerular filtration rate: implications for identifying chronic kidney disease. Curr Opin Nephrol Hypertens. 2007;16(3):242-9.

16. Myers GL, Miller WG, Coresh J, Fleming J, Greenberg N, Greene T, et al. Recommendations for improving serum creatinine measurement: a report from the Laboratory Working Group of the National Kidney Disease Education Program. Clin Chem. 2006;52(1):5-18.

17. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation for the Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-70.

18. Walser M, Drew HH, Guldan JL. Prediction of glomerular filtration rate from serum creatinine concentration in advanced chronic renal failure. Kidney Int. 1993;44(5):1145-8.

19. Marshall MR, Song Q, Ma TM, MacDonell SG, Kasabov NK. Evolving connectionist system versus algebraic formulas for prediction of renal function from serum creatinine. Kidney Int. 2005;67(5):1944-54.

20. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet. 1986;1:307-10.

21. Wyatt CM, Schwartz GJ, Ong'or WO, Abuya J, Abraham AG, Mboku C, et al. Estimating kidney function in HIV-infected adults in Kenya: comparison to a direct measure of glomerular filtration rate by iohexol clearance. PLoS One. 2013;8(8):e69601.

22. O'Keefe SJ, Chung D, Mahmoud N, *et al*. Why do African Americans get more colon cancer than Native Africans? J Nutr. 2007;137(1 Suppl):175S-82S.

23. King AJ, Levey AS. Dietary protein and renal function. J Am Soc Nephrol. 1993;3(11):1723-37.

24. Klahr S, Levey AS, Beck GJ, Caggiula AW, Hunsicker L, Kusek JW, et al. The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. Modification of Diet in Renal Disease Study Group. N Engl J Med. 1994;330(13):877-84.

25. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73(4):391-8.

26. Naicker S. Nutritional problems associated with end-stage renal disease in the developing world. Artif Organs. 2002;26(9):757-9.

27. Bärnighausen T, Welz T, Hosegood V, Bätzing-Feigenbaum J, Tanser F, Herbst K, et al. Hiding in the shadows of the HIV epidemic: obesity and hypertension in a rural population with very high HIV prevalence in South Africa. J Hum Hypertens. 2008;22(3):236-9.

28. Wand H, Ramjee G. High prevalence of obesity among women who enrolled in HIV prevention trials in KwaZulu-Natal, South Africa: healthy diet and life style messages should be integrated into HIV prevention programs. BMC Public Health. 2013;13(1):1.

Table 1. Prediction equations used to estimate glomerular filtration rate in adults

Prediction equation
Cockcroft-Gault equation (2) corrected to ml/min/1.73 m^2
eGFR (mL/min/1.73m2) = [(140 – age) × weight (kg) × 0.85 (if female) × 1.73 m^2] / [serum creatinine (μmol/L) × 0.814 × BSA (m^2)]
Four-variable MDRD equation (3)
eGFR (mL/min/1.73 m^2) = 175 × (Scr (μmol/L) / 88.4) $^{-1.154}$ × (age) $^{-0.203}$ × 0.742 (if female) × 1.212 (if African American)
CKD-EPI equation (4)
eGFR = 141 × min (Scr /κ, 1)$^{\alpha}$ × max (Scr /κ, 1)$^{-1.209}$ × 0.993^{Age} × 1.018 (if female) × 1.159 (if African American)
where:
Scr is serum creatinine in μmol/L
κ is 61.9 for females and 79.6 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

eGFR, estimated glomerular filtration rate; BSA, body surface area; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Table 2. Prediction equations obtained during the 3-phase development stages

	Equation
1	$86.8689 \times Scr^{-0.2814} \times Age^{-0.2929} \times Urea^{-0.2908} \times Alb^{0.4845}$
2	$27.3769 \times Scr^{-0.2439} \times Age^{-0.0667} \times Urea^{-0.3076} \times Alb^{0.5728}$
3	$106.4100 \times Scr^{-0.3239} \times Age^{-0.3851} \times Urea^{-0\ 2621} \times Alb^{0.5134}$

GFR, glomerular filtration rate; Scr, serum creatinine; Alb, serum albumin.

Table 3. Clinical and laboratory characteristics

Parameter	Total (n=76)	Male (n=23)	Female (n=53)	P-value
Age (years)	56 ± 14	55 ± 14	57 ± 14	0.677
Female, n (%)	53 (69.7)	----	----	----
Waist circumference (cm)	100.3 ± 13.7	98.4 ± 11.1	101 ± 14.6	0.446
Body mass index (kg/m^2)	31.0 ± 7.2	28.7 ± 7.5	32.0 ± 6.9	0.065
Systolic blood pressure (mmHg)	137.5 ± 23.4	132.7 ± 26.7	139.6 ± 21.7	0.239
Diastolic blood pressure (mmHg)	74.2 ± 15.8	74.3 ± 17.3	74.2 ± 15.3	0.993
*Glucose (mmol/l)	5.6 (2.6)	12.4 (3.1)	5.5 (2.3)	0.773
*Serum creatinine (µmol/l)	118 (79.5)	161 (118)	104 (53)	<0.001
*Urea (mmol/l)	7.1 (5.5)	8.1 (9.8)	7.0 (4.0)	0.178
^{99m}Tc-DTPA-mGFR (ml/min/1.73m^2)	51.3 ± 22.6	45.4 ± 18.7	53.9 ± 23.8	0.102
MDRD-eGFR (ml/min/1.73m^2)	45.1 ± 24.4	39.2 ± 18.1	47.6 ± 26.4	0.112
CKD EPI-eGFR (ml/min/1.73m^2)	47.8 ± 24.4	41.4 ± 20.4	50.5 ± 25.6	0.107
CG_BSA-eGFR (ml/min/1.73m^2)	56.8 ± 30.2	46.4 ± 21.5	61.2 ± 32.4	0.021
CG-eGFR (ml/min)	63.6 ± 34.7	53.3 ± 27.8	68.1 ± 36.7	0.059
*Urine ACR (mg/mmol)	9.1 (85.1)	20 (86.1)	8.5 (84.5)	0.977
Serum albumin (g/l)	36.0 ± 5.5	36.7 ± 5.9	35.8 ± 5.3	0.522

*Non-normal data summarized as median (IQR). ^{99m}Tc-DTPA; technicium-99m-diethylenetriaminepentaacetic acid; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CG, Cockcroft-Gault (*in ml/min); BSA, body surface area; ACR albumin: creatinine ratio.

Table 4. Agreement between estimated and measured glomerular filtration rate

eGFR equation	Mean bias (95% CI) (ml/min/1.73m^2)	RMSE (ml/min/1.73m^2)	95% limits of agreement	P_{30} (%)
*CG	-12.31 (-20.09, -4.54)	23.55	-58.46, 33.84	47.3
CG_BSA	-5.45 (-9.22, -1.68)	19.74	-44.1, 33.2	54.0
MDRD	6.21 (2.75, 9.67)	18.11	-29.29, 41.70	51.3
CKD-EPI	3.552 (0.27, 6.82)	17.10	-29.96, 37.06	63.2
Equation 1	1.79 (-0.78, 4.35)	13.41	-24.51, 28.08	78.95
Equation 2	2.40 (-0.33, 5.13)	14.26	-25.57, 30.37	72.37
Equation 3	1.66 (-0.89, 4.22)	13.36	-24.52, 27.84	75.00
African modified MDRD	-0.72 (-5.17, 3.73)	13.44	-27.06, 25.63	75.00

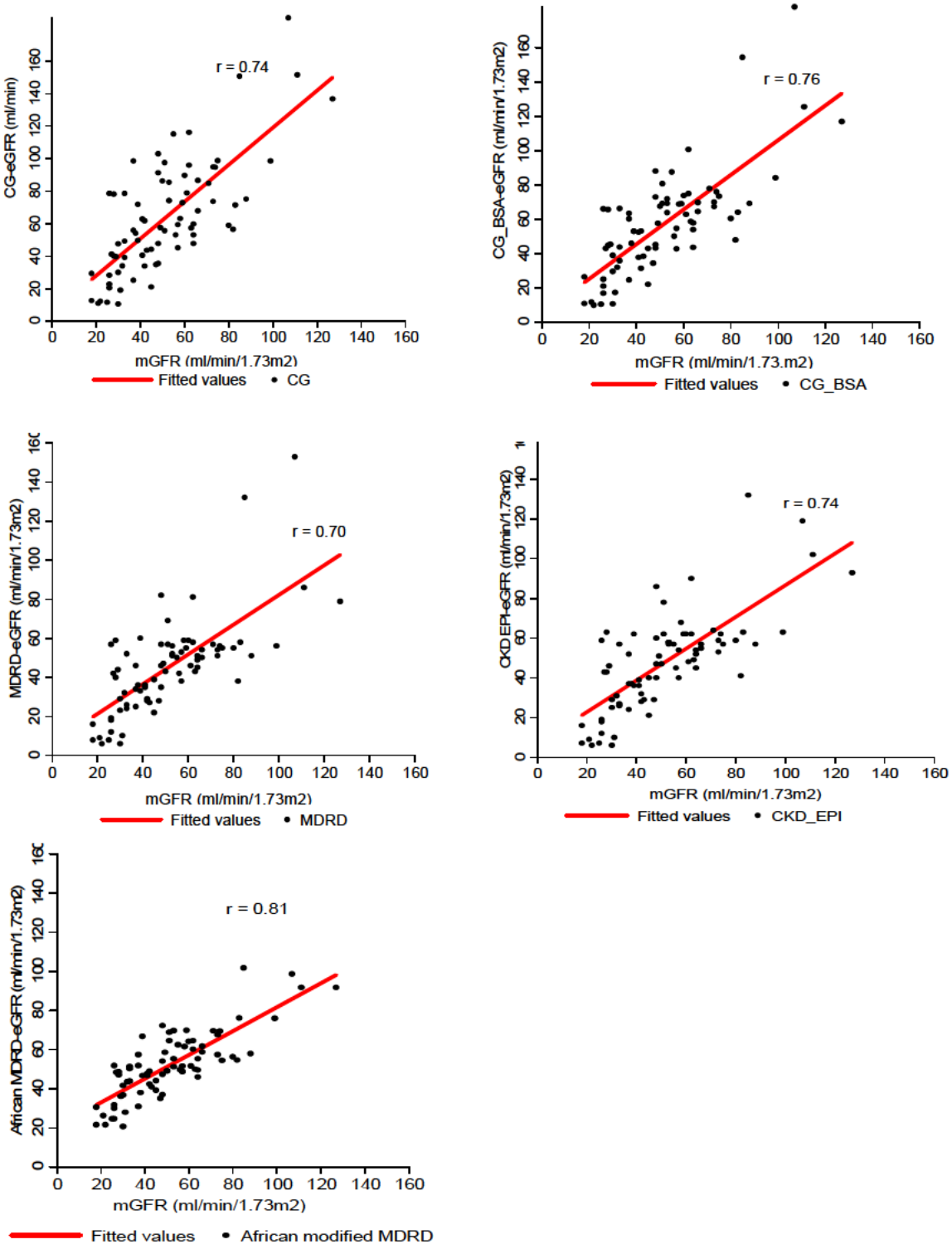
eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; CG, Cockcroft-Gault (*in ml/min); BSA, body surface area; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; RMSE, root mean square error; P_{30}, proportion of eGFR that fall within 30% of mGFR.

Table 5. Agreement between estimated and measured glomerular filtration rate in patients with different glomerular filtration rate categories

eGFR (ml/min/1.73m^2)	**N**	**Mean bias** (ml/min/1.73m^2)	**RMSE** (ml/min/1.73m^2)
*CG			
Overall	76	-12.31 (-20.09, -4.54)	23.55
<30	12	8.43 (2.46, 14.40)	9.40
30-60	29	-0.28 (-4.80, 4.24)	11.89
≥60	35	-29.39 (37.09, 21.69)	22.42
CG_BSA adjusted			
Overall	76	-5.45 (-9.22, -1.68)	19.74
<30	13	9.16 (4.11, 14.2)	8.36
30-60	28	0.60 (-4.63, 5.8)	12.35
≥60	35	-15.30 (-23.04, 7.57)	22.51
MDRD			
Overall	76	6.21 (2.75, 9.67)	18.11
<30	20	12.60 (9.60, 15.60)	6.41
30-60	48	6.92 (2.33, 11.51)	15.81
≥60	8	-14.0 (-42.21, 14.21)	33.73
CKD-EPI			
Overall	76	3.55 (0.27, 6.82)	17.10
<30	19	12.37 (9.08, 15.67)	6.83
30-60	38	4.34 (-0.45, 9.13)	14.57
≥60	19	-6.84 (-18.02, 4.33)	23.19
African modified			
Overall	76	-0.72 (-3.79, 2.35)	13.44
<30	7	0.83 (-3.57, 5.22)	4.75
30-60	48	-0.52 (-4.41, 3.38)	13.42
≥60	21	-1.70 (-.8.83, 5.43)	15.67

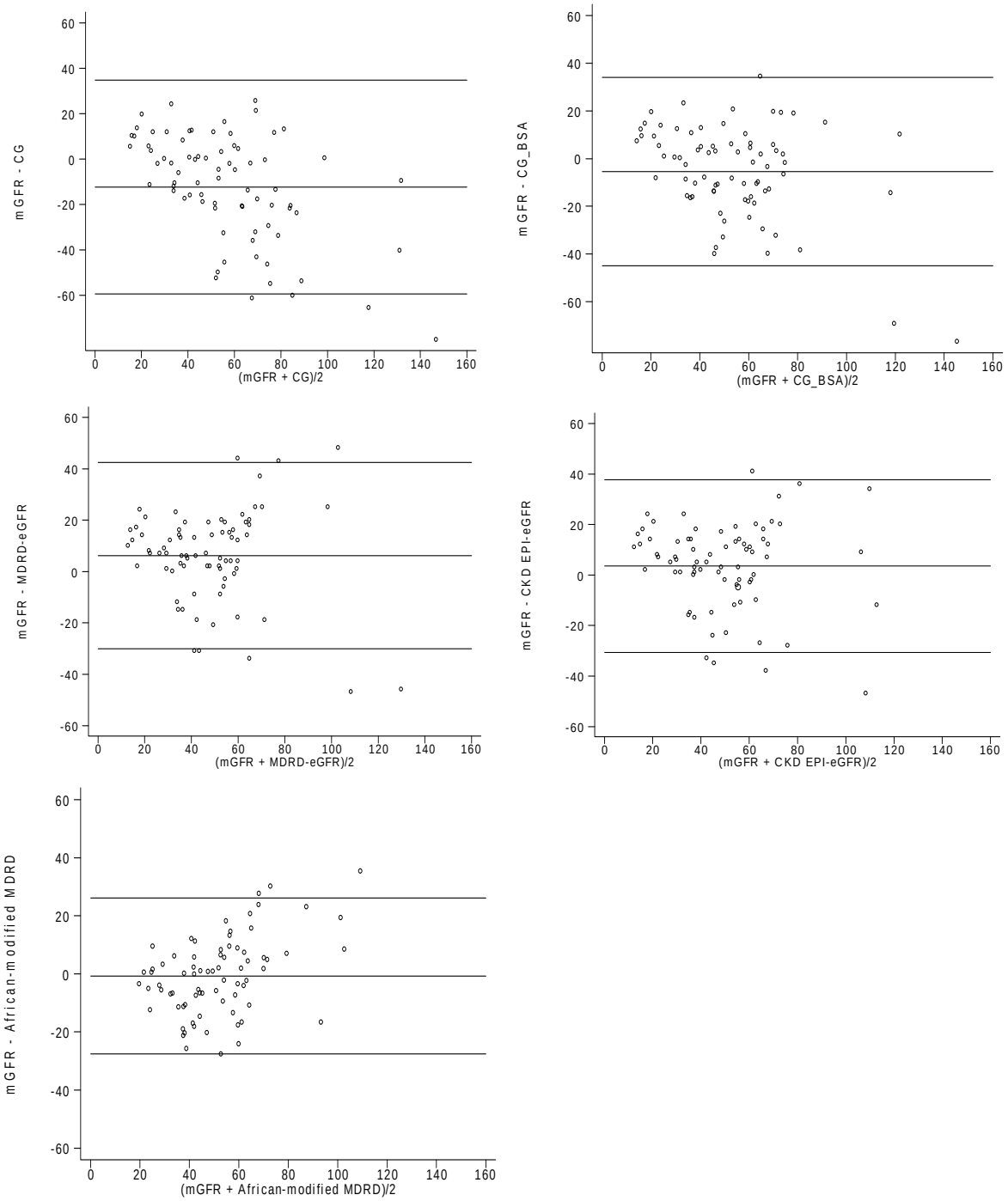
eGFR, estimated glomerular filtration rate; mGFR, measured glomerular filtration rate; N, number; CG, Cockcroft-Gault (*in ml/min); BSA, body surface area; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; RMSE, root mean square error.

Figure 1. Correlation between estimated and measured glomerular filtration rate.



eGFR, estimated glomerular filtration rate, mGFR, measured glomerular filtration rate, CG, Cockcroft-Gault (*in ml/min); BSA, body surface area; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

Figure 2. Agreement between measured and estimated glomerular filtration rate by CG, CKD-EPI, MDRD as well as African modified MDRD equations.



CG, Cockcroft-Gault (*in ml/min); BSA, body surface area; MDRD, Modification of Diet in Renal Disease; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration.

CHAPTER 8

DISCUSSION AND CONCLUSION

8.1. SYNTHESIS OF KEY FINDINGS

The work presented in this thesis provides an observational profile of CKD patients at two regional (secondary) level hospital sites outside of a tertiary level nephrologist-run setting. Each chapter presents novel findings on aspects of the epidemiology of CKD at earlier stages, before dialysis is reached, adding substantially to the understanding of non-dialysis dependant CKD in a patient population that has not been widely studied. Chapters 2-5 comprise studies of risk factors and complications, while chapters 6 and 7 investigated diagnostic methods.

8.1.1. RISK FACTORS ASSOCIATED WITH CHRONIC KIDNEY DISEASE AND CARDIOVASCULAR DISEASE

Chapter 2 describes patients presenting at a regional level hospital-based outreach CKD clinic in rural northern KwaZulu-Natal. Chapters 3-5 describe patients at a regional hospital-based clinic serving urban and peri-urban areas of Durban. About 90% of patients were of African ancestry, reflecting hospital patient demographics at both study sites and two-thirds were female. Patients with CKD in our setting are young (<60 years old). The profile of these cohorts resembles CKD in poor urban vulnerable populations in the US public health system who are also young (59 ± 13.8 years), mainly non-white and at greater risk for CKD progression (74).

Hypertension, diabetes mellitus and HIV were the major CKD risk factors in both rural and urban sites thus, CKD is largely associated with modifiable risk factors in our population. We reaffirmed the observation by others of the leading role of hypertension as the commonest CKD risk factor in South Africa, which was observed in 75% in northern KwaZulu-Natal and 73% in the Durban site; with prevalence of ~50% in those with eGFR ≥90 ml/min/1.73m^2 that increased with each subsequent CKD stage to ~90% when eGFR was <30 ml/min/1.73m^2. Diabetes was found in ~30% of patients (29.8% and 27.6% in northern KwaZulu-Natal and Durban, respectively). Therefore, our hypothesis that diabetes would be the commonest contributor to the CKD burden, based on global data, was rejected in both cohorts. Nonetheless, its emergence as the second commonest risk factor is significant as it heralds the potential future increase in the burden of diabetic ESRD. The rising trend is well under way, as diabetes accounted for 12.4% of ESRD cases in the latest South African Renal Registry Report (19) versus the 1994 Report (6) that made no reference to diabetes.

We expected HIV infection to be a major contributor to the CKD burden owing to its high prevalence in the province of KwaZulu-Natal as the HIV epicentre in South Africa. Its emergence as the third commonest CKD risk factor could mark a shift in the role of infections in the pathogenesis of CKD locally. Prevalence of HIV infection was higher in the northern KwaZulu-Natal outreach cohort (~30%) vs <20% in the Durban cohort, suggesting an association between HIV infection and rural location. Although HIV prevalence in this region is well-documented, data on the burden of CKD in HIV are lacking. A primary level healthcare study in northern KwaZulu-Natal found CKD in 14.4% of HIV patients but <1.5% had severe CKD or eGFR <30 ml/min/1.73m^2 (75). In our outreach cohort (Chapter 2), HIV was a strong independent predictor of severe CKD. Prospective studies assessing CKD progression rates in HIV patients are needed to establish causality. While antiretroviral therapy will reduce the incidence of HIVAN, the CKD burden in HIV is likely to rise in South Africa as hypertensive as well as diabetic CKD increase due to improved patient survival and treatment-related adverse cardiometabolic effects.

Glomerulonephritis unrelated to HIV was uncommon at both rural and urban sites, except in the eGFR validation study (Chapter 7) where 40% of patients had glomerulonephritis, as the most prevalent CKD cause. The high prevalence in that group reflects the study setting, which was a specialist nephrologist clinic as well as the practice of referring glomerulonephritis patients to nephrologists for renal biopsy and management. Another highly prevalent modifiable risk factor was obesity, with >80% of females and almost 60% males in the northern KwaZulu-Natal as well as the Durban site, overweight/obese. This was similar to the high population prevalence reported in rural (76) and urban (77) KwaZulu-Natal as well as in high CVD risk patients studied elsewhere in South Africa (78). The data reflect the epidemiological transition into diseases of lifestyle occurring in South Africa as in other developing countries. The distribution of CKD, CVD or other CVD risk markers associated with obesity, showed no gender preponderance; only dyslipidaemia was twice as common in females than in males in the northern KwaZulu-Natal cohort but not in the Durban cohort.

8.1.2. RISK FACTORS FOR PROGRESSION OF CHRONIC KIDNEY DISEASE

Chapters 2 and 3 also showed that albuminuria was highly prevalent (>40% of patients), which together with hypertension, are major risk factors for CKD progression while treatment of both is renoprotective (79-82). Based on evidence for this central role in CKD progression, KDIGO guidelines recommend ACE inhibitor or ARB use and blood pressure control in patients with albuminuria (2). Sixty percent of patients at both sites were on either an ACE inhibitor or ARB at presentation to secondary healthcare level. Both drug classes are available at primary healthcare level in South Africa and are included in the South African Hypertension Guidelines as first line therapy, with CKD an added indication for their use (83). Notwithstanding the availability of these renoprotective drugs, >70% of patients at the outreach site and almost 40% at the Durban site had CKD stage ≥3 at initial visit. Thus, prospective studies are needed to investigate causal factors particularly, rapid CKD progression or delayed referral from primary level healthcare.

8.1.3. COMPLICATIONS ASSOCIATED WITH CHRONIC KIDNEY DISEASE

Chapter 3 evaluated CKD and CVD risk factors in the Durban patients. This study presents further novel findings in a South African cohort, of highly prevalent hyperuricaemia, with central obesity, declining eGFR as well as albuminuria as strong independent predictors. Although hyperuricaemia is well-recognized as a consequence of CKD, its presence in 16.7% of patients with eGFR ≥90 ml/min/1.73m^2 is of particular interest as this group might be at risk for incident CKD and may need follow-up. Interventional studies of urate-lowering therapy with allopurinol in such patients are needed to evaluate the potential benefits of urate-lowering on primary or secondary CKD prevention since evidence on renal outcomes remains unclear. Prevalence of hyperuricaemia, in association with gout, is increasing globally, in parallel to the obesity epidemic (39, 84, 85). Interestingly, hyperuricaemia in our cohort was associated with a low, rather than high, gout prevalence and African ancestry was seemingly protective against gout. This unique finding was unexpected and contrary to observations in African Americans who have a high risk for both (39). The low prevalence in our cohort might reflect lower protein intake since dietary protein intake was found to be lower in indigenous South Africans compared to African Americans (86). High protein intake is among the factors implicated in the rising prevalence of hyperuricaemia and gout with Western lifestyles (87). However, our study did not evaluate dietary intake.

In the study of CKD-related metabolic and endocrine abnormalities (Chapter 4), we found a high frequency of metabolic acidosis (21%), anaemia (19%), hyperphosphataemia (14%) as well as hypocalcaemia (5%) compared to observations in CKD patient cohorts in other published studies. Some, like hyperuricaemia, were prevalent even at high eGFR levels. The finding of disorders usually associated with later CKD stages, in early CKD in our patient population, has not been reported in South Africans previously and is similar to findings in African Americans and European Africans. This implies a need for the training of non-nephrologists in tertiary CKD prevention strategies in our setting and extending access to specific pharmacological therapies for these disorders to patients at regional level clinics managed by non-nephrologists. As expected, prevalence of each disorder increased significantly as eGFR declined, and more so when eGFR was <45 ml/min/1.73m^2. The risk for adverse outcomes rises sharply below this GFR level, hence the need for close monitoring once patients reach stage 3b CKD.

Another complication of CKD that is strongly associated with adverse outcomes is PEW. We postulated that PEW would be common in our patient population following previously cited findings in South Africans that dietary protein intake, a component of the PEW syndrome, was low in healthy volunteers (86) and prevalence of malnutrition was high in CAPD patients (88). Chapter 5 evaluated the association of markers of PEW with ^{99m}Tc-DTPA mGFR, for the first time in an African cohort of non-dialysis CKD patients and showed that males had significantly lower lean and fat mass at lower mGFR levels (CKD stage ≥3b), which was not seen in females. This and the disproportionately higher risk of malnutrition in males in the cited CAPD study, implies that serial longitudinal evaluation of body composition changes over time is needed to confirm lean mass as well as fat loss and that nutritional surveillance must be considered early in the course of CKD in males.

8.1.4. ESTIMATION OF GLOMERULAR FILTRATION RATE FOR DETECTION OF CHRONIC KIDNEY DISEASE

Primary, secondary and tertiary prevention to reduce complications in CKD, requires cost-effective tools for CKD screening and diagnosis, hence the reliance on serum creatinine-based equations for GFR estimation in routine clinical decision-making. These equations were developed in Europe and North America therefore require validation in other populations. We undertook such a validation study (Chapter 6) by evaluating eGFR performance in predicting

^{99m}Tc-DTPA-mGFR. Our results confirmed the findings of two prior studies that eGFR equations were inaccurate in Africans and overestimated mGFR (72) or 24-hour creatinine clearance (73), with better prediction after omitting the African American derived correction factors for black ethnicity, which we also found.

These data prompted our effort to develop an equation in patients of African ancestry from demographic and biochemical variables using methods described in developing the MDRD equation as presented in Chapter 8. We postulated that this new equation would predict ^{99m}Tc-DTPA-mGFR better than the CG, MDRD and CKD-EPI equations (64, 65, 67), which we subsequently showed as the new equation had the lowest bias, best precision, highest accuracy and correlation to mGFR compared to existing equations. This African equation is a novel and significant advance towards achieving more accurate GFR prediction in black Africans thus, it holds great promise as a tool for CKD diagnosis in future. Prediction of GFR by the existing 3 equations was comparable in this study with that of prior studies. Interestingly, our previous observation that eGFR underestimated mGFR in stages 4 and 5 CKD (Chapter 6) were again evident in this study, further raising the possibility of increased muscle catabolism and creatinine generation in severe CKD in this patient population that awaits future investigation.

8.2. STUDY LIMTATIONS

The cross-sectional design used in the studies contained in this thesis was useful in the evaluation of key epidemiological aspects of CKD in our study patient population, in the absence of population data. Various associations were reported and several hypotheses for future studies were generated. However, causal inferences cannot be made from the observed associations, which is the major limitation of this study design. Selection bias is a potential limitation of the study setting in hospital-based clinics since the study participants are unlikely to be representative of the general population. Misdiagnosis in assigning comorbidities might have occurred with the use of self-reported diagnosis, current medication, prior clinical and pharmacy records. Another potential source of misclassification is the use of eGFR equations, leading to errors in CKD staging. The small sample size of the studies and absence of appropriate control groups in each of the studies, as a consequence of limited funding, might affect the reliability of the results thus, are further limitations. Future studies are needed, with sufficient power and control groups, e.g. healthy controls as well as rural/urban patients to overcome the identified limitations.

8.3. CONCLUSIONS AND RECOMMENDATIONS

This work provides evidence that CKD affects relatively young patients and is associated with multiple comorbidities in adults seen at two regional hospital-based clinics, with limited access to nephrologists, cardiologists or diabetologists or other subspecialists. We confirmed that hypertension remains the commonest CKD risk factor, which is prevalent across the CKD spectrum, often with comorbidities like diabetes, HIV, CVD and obesity. This calls for intensified efforts aimed at early diagnosis and effective management of hypertension. Lessons could be obtained from the successful National Blood Pressure Education Program in USA, a private-public partnership designed to motivate the public, physicians, nurses, pharmacists and other health workers to do a better job of managing hypertension, which resulted in markedly improved hypertension awareness, treatment and control as well as reduced mortality (89). Diabetes and HIV were shown to be emerging in our setting as important contributors to the CKD burden. Both are likely to change the epidemiology of ESRD in future due to recent favourable changes in RRT acceptance criteria in South Africa, which are now more inclusive of diabetic and HIV patients.

We have also shown that CKD-related metabolic and endocrine complications were prevalent, mainly from CKD stage ≥3b but also at normal GFR levels, with patients often untreated for these complications. This could either reflect resource-management policies that restrict treatment availability only to subspecialty clinics or lack of awareness of treatment and/or the resultant benefits, except in the case of hyperuricaemia, where evidence on the benefits of urate-lowering is inconclusive. The observed unexpected negative association of gout with African ancestry needs further evaluation. We further suggest PEW as another complication that might occur early, especially in males, who were found to have reduced lean and fat mass from CKD stage ≥3b however, we could not assess longitudinal changes in lean and fat mass with the present study design.

This observation in males as well as that of mGFR underestimation by eGFR in stages 4 and 5 CKD patients in the two GFR estimation studies, raises a possibility of increased catabolism in our population that could affect GFR estimation; a potential subject for future research. In addition, we found that eGFR overestimated mGFR in earlier CKD stages in both studies. These extremes in GFR estimation were substantially minimized, by the equation that was developed in

Africans, albeit not eliminated. Nevertheless, we have concluded that the improved accuracy seen with the new equation, which showed better GFR prediction than existing ones, warrants more effort to further develop and validate it in a large study sample comprising a wide range of GFR values. Attempts to build on this innovation by establishing a network of investigators and planning a large multicentre study of Africans are underway. A major hurdle is the unavailability of radioisotope studies in many public healthcare centres in South Africa and lack of uniformity in the clearance agent used in the few that offer radioisotope GFR. This will necessitate collaboration with the private healthcare sector and researchers in other African countries.

The antiretroviral therapy roll-out program provides a practical framework through which training of primary healthcare doctors and nurses was performed successfully in South Africa. The program, based at primary healthcare level with minimal specialist/subspecialist support, has delivered much needed treatment to multitudes of HIV patients many of whom likely had complex co-existing diseases, including infections and malignancies. We recommend adoption of a similar national strategy to train primary and regional level healthcare practitioners in primary, secondary as well as tertiary prevention, which we plan to propose to relevant health stakeholders to reduce the impact of CKD. Specialist outreach programs bring valuable expertise to primary healthcare practitioners and patients; hence it is commendable that outreach services to northern KwaZulu-Natal by specialists from both public and private healthcare sector in Durban have slowly gained traction over the last two years. Lobbying of health authorities, to extend provision of effective therapies to lower levels of care is indeed warranted, especially to areas without specialists/subspecialists or where there is no option for up-referral and/or RRT.

Lastly, the data presented underscore a need for population studies and registries to provide data on the various aspects of CKD. Studies of high-risk individuals are valuable to obtain epidemiological data, to understand disease patterns and distribution as well as guide resource allocation, where population studies are not feasible. A diagnostic method developed and validated in the population in which it will be used is necessary to provide a more accurate estimate of the GFR level.

REFERENCES

REFERENCES

1. National Kidney Foundation - K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. Am J Kidney Dis. 2002;39 (suppl 2):S1-S246.

2. Kidney Disease Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO Clinical Practice Guideline for the Evaluation and Management of chronic kidney disease. Kidney Int Suppl. 2012;3(1):1-150.

3. Schieppati A, Remuzzi G. Chronic renal diseases as a public health problem: Epidemiology, social and economic implications. Kidney Int. 2005;68(Suppl 98):S7-S10.

4. Sarnak MJ, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: a statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension. 2003;42(5):1050-65.

5. Dirks JH, De Zeeuw D, Agarwal SK, *et al*. Prevention of chronic kidney and vascular disease: Toward global health equity - The Bellagio 2004 Declaration. Kidney Int. 2005;68(Suppl 98):S1-S6.

6. Naicker S. End-stage renal disease in sub-Saharan and South Africa. Kidney Int. 2003;63(Suppl 83):119-22.

7. Abu-Aisha H, Elamin S. Peritoneal dialysis in Africa. Perit Dial Int. 2010;30:23-8.

8. Davids MR, Marais N, Jacobs JC. South African Renal Registry Annual Report 2015. African Journal of Nephrology. 2017;20(1):201-13.

9. Atkins RC, Zimmet P. Diabetic kidney disease: act now or pay later. Acta Diabetol. 2010;47:1-4.

10. Naicker S. Challenges for nephrology practice in Sub-Saharan Africa. Nephrol Dial Transplant. 2010;25:649-50.

11. Moosa MR, Kidd M. The dangers of rationing dialysis treatment: the dilemma facing a developing country. Kidney Int. 2006;70(6):1107-14.

12. Arogundade FA, Barsoum RS. CKD prevention in Sub-Saharan Africa: a call for governmental, nongovernmental, and community support. Am J Kidney Dis. 2008;51(3):515-23.

13. Bhimma R, Coovadia HM. Hepatitis B virus-associated nephropathy. Am J Nephrol. 2004;24(2):198-211.

14. Bhimma R, Coovadia HM, Adhikari M, Connolly CA. The impact of the hepatitis B virus vaccine on the incidence of hepatitis B virus–associated membranous nephropathy. Arch Pediatr Adolesc Med. 2003;157(10):1025-30.

15. Olowu WA, Adelusola KA, Adefehinti O, Oyetunji TG. Quartan malaria-associated childhood nephrotic syndrome: now a rare clinical entity in malaria endemic Nigeria. Nephrol Dial Transplant. 2010;25(3):794-801.

16. South African Renal Society, South African Transplant Society, Southern African HIV Clinicians Society. Guidelines for renal replacement therapy in HIV-infected individuals in South Africa. South Afr J HIV Med. 2008;Autumn:34-42.

17. Han TM, Naicker S, Ramdial PK, Assounga AGH. A cross-sectional study of HIV-seropositive patients with varying degrees of proteinuria in South Africa. Kidney Int. 2006;69(12):2243-50.

18. Madala N, Naicker S, Singh B, et al. The pathogenesis of membranoproliferative glomerulonephritis in KwaZulu-Natal, South Africa is unrelated to hepatitis C virus infection. Clin Nephrol. 2003;60:69-73.

19. Davids MR, Marais N, Jacobs JC. South African Renal Registry Annual Report 2012. http://www.sa-renalsociety.org 2012.

20. Zhang Q-L, Rothenbacher D. Prevalence of chronic kidney disease in population-based studies: Systematic review. BMC Public Health. 2008;8(117).

21. Easterling R. Racial factors in the incidence and causation of end stage renal disease. Trans Am Soc Artif Intern Organs. 1977;23:28-32.

22. Tomson CR, Foley RN, Li Q, Gilbertson DT, Xue JL, Collins AJ. Race and end-stage renal disease in the United States Medicare population: the disparity persists Nephrology. 2008;13(7):651-6.

23. The ESRD Incidence Study Group: Geographic, ethnic, age-related and temporal variation in the incidence of end-stage renal disease in Europe, Canada and the Asia-Pacific region, 1998-2002. Nephrol Dial Transplant. 2006;21:2178-83.

24. Genovese G, Friedman DJ, Pollak MR. APOL1 variants and kidney disease in people of recent African ancestry. Nat Rev Nephrol. 2013;9(4):240-4.

25. Kasembeli AN, Duarte R, Ramsay M, Mosiane P, Dickens C, Dix-Peek T, et al. APOL1 risk variants are strongly associated with HIV-associated nephropathy in black South Africans. J Am Soc Nephrol. 2015;26(11):2882-90.

26. Taal M, Brenner B. Predicting initiation and progression of chronic kidney disease: Developing renal risk scores Kidney Int. 2006;70:1694-705.

27. McClellan WM, Jurkovitz C, Abramson J. The epidemiology and control of anaemia among pre-ESRD patients with chronic kidney disease. Eur J Clin Invest. 2005;35 Suppl 3:58-65.

28. Inrig JK, Barnhart HX, Reddan D, Patel UD, Sapp S, Califf RM, et al. Effect of hemoglobin target on progression of kidney disease: a secondary analysis of the CHOIR (Correction of Hemoglobin and Outcomes in Renal Insufficiency) trial. Am J Kidney Dis. 2012;60(3):390-401.

29. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006;1(4):825-31.

30. Covic A, Kothawala P, Bernal M, Robbins S, Chalian A, Goldsmith D. Systematic review of the evidence underlying the association between mineral metabolism disturbances and risk of all-cause mortality, cardiovascular mortality and cardiovascular events in chronic kidney disease. Nephrol Dial Transplant. 2009;24(5):1506-23.

31. Scialla JJ, Astor BC, Isakova T, Xie H, Appel LJ, Wolf M. Mineral metabolites and CKD progression in African Americans. J Am Soc Nephrol. 2013;24(1):125-35.

32. Shah SN, Abramowitz M, Hostetter TH, Melamed ML. Serum bicarbonate levels and the progression of kidney disease: a cohort study. Am J Kidney Dis. 2009;54(2):270-7.

33. Phisitkul S, Khanna A, Simoni J, Broglio K, Sheather S, Rajab MH, et al. Amelioration of metabolic acidosis in patients with low GFR reduced kidney endothelin production and kidney injury, and better preserved GFR. Kidney Int. 2010;77(7):617-23.

34. Mahajan A, Simoni J, Sheather SJ, Broglio KR, Rajab MH, Wesson DE. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int. 2010;78(3):303-9.

35. Susantitaphong P, Sewaralthahab K, Balk EM, Jaber BL, Madias NE. Short- and long-term effects of alkali therapy in chronic kidney disease: a systematic review. Am J Nephrol. 2012;35(6):540-7.

36. Johnson RJ, Nakagawa T, Jalal D, Sanchez-Lozada LG, Kang DH, Ritz E. Uric acid and chronic kidney disease: which is chasing which? Nephrol Dial Transplant. 2013;28(9):2221-8.

37. Rosolowsky ET, Ficociello LH, Maselli NJ, Niewczas MA, Binns AL, Roshan B, et al. High-normal serum uric acid is associated with impaired glomerular filtration rate in nonproteinuric patients with type 1 diabetes. Clin J Am Soc Nephrol. 2008;3(3):706-13.

38. Chen N, Wang W, Huang Y, Shen P, Pei D, Yu H, et al. Community-based study on CKD subjects and the associated risk factors. Nephrol Dial Transplant. 2009;24(7):2117-23.

39. Krishnan E. Reduced glomerular function and prevalence of gout: NHANES 2009-10. PLoS One. 2012;7(11):e50046.

40. Li L, Yang C, Zhao Y, Zeng X, Liu F, Fu P. Is hyperuricemia an independent risk factor for new-onset chronic kidney disease? A systematic review and meta-analysis based on observational cohort studies. BMC Nephrol. 2014;15(1):122.

41. Yamada T, Fukatsu M, Suzuki S, Wada T, Joh T. Elevated serum uric acid predicts chronic kidney disease. Am J Med Sci. 2011;342(6):461-6.

42. Levin A. Clinical epidemiology of cardiovascular disease in chronic kidney disease prior to dialysis. Semin Dial. 2003;16(2):101-5.

43. Wheeler DC, Townend JN, Landray MJ. Cardiovascular risk factors in predialysis patients: baseline data from the Chronic Renal Impairment in Birmingham (CRIB) study. Kidney International Supplement. 2003(84):S201-3.

44. Jungers P, Massy Z, Khoa TN, Fumeron C, Labrunie M, Lacour B, et al. Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study. Nephrol Dial Transplant. 1997;12(12):2597-602.

45. Manjunath G, Tighiouart H, Ibrahim H, MacLeod B, Salem DN, Griffith JL, et al. Level of kidney function as a risk factor for atherosclerotic cardiovascular outcomes in the community. J Am Coll Cardiol. 2003;41(1):47-55.

46. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu C-y. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. N Engl J Med. 2004;351(13):1296-305.

47. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, Quinn RR, et al. Relation between kidney function, proteinuria, and adverse outcomes. JAMA. 2010;303(5):423-9.

48. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality: a collaborative meta-analysis of general population cohorts. Lancet. 2010;375(9731):2073.

49. Alebiosu CO, Odusan O, Familoni OB, Jaiyesimi AEA. Cardiovascular risk factors in type 2 diabetic Nigerians with clinical diabetic nephropathy. Cardiovasc J S Afr. 2004;15(3):124-8.

50. Amira OC, Naicker S, Manga P, Sliwa K, Mia A, Raal F, et al. Adiponectin and atherosclerosis risk factors in African hemodialysis patients: a population at low risk for atherosclerotic cardiovascular disease. Hemodial Int. 2012;16(1):59-68.

51. Eghan BA, Amoako-Atta K, Kankam CA, Nsiah-Asare A. Survival pattern of hemodialysis patients in Kumasi, Ghana: a summary of forty patients initiated on hemodialysis at a new hemodialysis unit. Hemodial Int. 2009;13(4):467-71.

52. Ulasi II, Arodiwe EB, Ijoma CK. Left ventricular hypertrophy in African Black patients with chronic renal failure at first evaluation. Ethn Dis. 2006;16(4):859.

53. Bayauli MP, Lepira FB, Kayembe PK, M'Buyamba-Kabangu JR. Left ventricular hypertrophy and geometry in type 2 diabetes patients with chronic kidney disease. An echocardiographic study. Cardiovasc J Afr. 2012;23(2):73-7.

54. Chijioke A, Makusidi AM, Kolo PM. Electrocardiographic abnormalities among dialysis naive chronic kidney disease patients in Ilorin Nigeria. Ann Afr Med. 2012;11(1):21-6.

55. Shibiru T, Gudina EK, Habte B, Derbew A, Agonafer T. Survival patterns of patients on maintenance hemodialysis for end stage renal disease in Ethiopia: summary of 91 cases. BMC Nephrol. 2013;14:127.

56. Comty CM. A longitudinal study of body composition in terminal uremics treated by regular hemodialysis. I. Body composition before treatment. Can Med Assoc J. 1968;98(10):482-91.

57. Coles GA. Body composition in chronic renal failure. Q J Med. 1972;41(161):25-47.

58. Fouque D, Kalantar-Zadeh K, Kopple J, Cano N, Chauveau P, Cuppari L, et al. A proposed nomenclature and diagnostic criteria for protein–energy wasting in acute and chronic kidney disease. Kidney Int. 2008;73(4):391-8.

59. Dukkipati R, Kopple JD. Causes and prevention of protein-energy wasting in chronic kidney failure. Semin Nephrol. 2009;29(1):39-49.

60. Kovesdy CP, Kopple JD, Kalantar-Zadeh K. Management of protein-energy wasting in non-dialysis-dependent chronic kidney disease: reconciling low protein intake with nutritional therapy. Am J Clin Nutr. 2013;97(6):1163-77.

61. Kopple JD, Greene T, Chumlea WC, Hollinger D, Maroni BJ, Merrill D, et al. Relationship between nutritional status and the glomerular filtration rate: results from the MDRD study. Kidney Int. 2000;57(4):1688-703.

62. Stenvinkel P, Heimburger O, Paultre F, Diczfalusy U, Wang T, Berglund L, et al. Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. Kidney Int. 1999;55(5):1899-911.

63. Carrero JJ, Stenvinkel P, Cuppari L, Ikizler TA, Kalantar-Zadeh K, Kaysen G, et al. Etiology of the protein-energy wasting syndrome in chronic kidney disease: a consensus statement from the International Society of Renal Nutrition and Metabolism (ISRNM). J Ren Nutr. 2013;23(2):77-90.

64. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16:31-41.

65. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation for the Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999;130:461-70.

66. Levey AS, Greene T, Kusek J, *et al*. A simplified equation to predict glomerular filtration rate from serum creatinine (abstract). J Am Soc Nephrol. 2000;11:155A.

67. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

68. Levey AS, Eckardt KU, Tsukamoto Y, Levin A, Coresh J, Rossert J, et al. Definition and classification of chronic kidney disease: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2005;67(6):2089-100.

69. Ma YC, Zuo L, Chen JH, *et al*. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol. 2006;17(10):2937-44.

70. Imai E, Horio M, Nitta K, *et al*. Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol. 2007;11(1):41-50.

71. Jafar TH, Schmid CH, Levey AS. Serum creatinine as marker of kidney function in South Asians: a study of reduced GFR in adults in Pakistan. J Am Soc Nephrol. 2005;16:1413-9.

72. Van Deventer HE, George JA, Paiker JE, Becker PJ, Katz IJ. Estimating glomerular filtration rate in black South Africans by use of the Modification of Diet in Renal Disease and Cockcroft-Gault equations. Clin Chem. 2008;54(7):1197-202.

73. Eastwood JB, Kerry SM, Plange-Rhule J, *et al*. Assessment of GFR by four methods in adults in Ashanti, Ghana: the need for an eGFR equation for lean African populations. Nephrol Dial Transplant. 2010:1-10.

74. Hall YN, Choi AI, Chertow GM, Bindman AB. Chronic kidney disease in the urban poor. Clin J Am Soc Nephrol. 2010;5(5):828-35.

75. Franey C, Knott D, Barnighausen T, Dedicoat M, Adam A, Lessells RJ, et al. Renal impairment in a rural African antiretroviral programme. BMC Infect Dis. 2009;9:143.

76. Bärnighausen T, Welz T, Hosegood V, Bätzing-Feigenbaum J, Tanser F, Herbst K, et al. Hiding in the shadows of the HIV epidemic: obesity and hypertension in a rural population with very high HIV prevalence in South Africa. J Hum Hypertens. 2008;22(3):236-9.

77. Wand H, Ramjee G. High prevalence of obesity among women who enrolled in HIV prevention trials in KwaZulu-Natal, South Africa: healthy diet and life style messages should be integrated into HIV prevention programs. BMC Public Health. 2013;13(1):1.

78. Katz I, Schneider H, Shezi Z, Mdleleni G, Gerntholtz T, Butler O, et al. Managing type 2 diabetes in Soweto--The South African Chronic Disease Outreach Program experience. Prim Care Diabetes. 2009;3(3):157-64.

79. Peterson J, Adler S, Burkart J. Blood pressure control, proteinuria and the progression of renal disease. Ann Intern Med. 1995;123:754-62.

80. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. N Engl J Med. 1993;329(20):1456-62.

81. Randomised placebo-controlled trial of effect of ramipril on decline in glomerular filtration rate and risk of terminal renal failure in proteinuric, non-diabetic nephropathy. The GISEN Group (Gruppo Italiano di Studi Epidemiologici in Nefrologia). Lancet. 1997;349(9069):1857-63.

82. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001; 345:861-9.

83. Seedat Y, Rayner B. South African Hypertension Guideline 2011: guideline. S Afr Med J. 2012;102(1):60-2, 4, 6-8, 70-83.

84. Kuo CF, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Ann Rheum Dis. 2014:doi:10.1136/annrheumdis-2013-204463.

85. Robinson PC, Taylor WJ, Merriman TR. Systematic review of the prevalence of gout and hyperuricaemia in Australia. Intern Med J. 2012;42(9):997-1007.

86. O'Keefe SJ, Chung D, Mahmoud N, *et al*. Why do African Americans get more colon cancer than Native Africans? J Nutr. 2007;137(1 Suppl):175S-82S.

87. Rho YH, Zhu Y, Choi HK. The epidemiology of uric acid and fructose. Semin Nephrol. 2011;31(5):410-9.

88. Naicker S. Nutritional problems associated with end-stage renal disease in the developing world. Artif Organs. 2002;26(9):757-9.

89. Moser M, Roccella EJ. The treatment of hypertension: a remarkable success story. Journal of clinical hypertension. 2013;15(2):88-91.

APPENDIX

UNIVERSITY OF
KWAZULU-NATAL
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RESEARCH OFFICE
BIOMEDICAL RESEARCH ETHICS ADMINISTRATION
Westville Campus
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Email: BREC@ukzn.ac.za
Website: http://research.ukzn.ac.za/ResearchEthics/BtomedicalResearchEthics.aspx

12 June 2012

Dr. ND Madala
Department of Nephrology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Madala

PROTOCOL: Chronic Kidney Disease in KwaZulu-Natal: Epidemiology, Pathogenesis and outcome. REF: BE179/11

EXPEDITED APPLICATION

A sub-committee of the Biomedical Research Ethics Committee has considered and noted your application received on 13 September 2011.

The study was provisionally approved pending appropriate responses to queries raised. Your responses dated 05 June 2012 to queries raised 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 12 June 2012.

This approval is valid for one year from 12 June 2012. 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 (2004), 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 11415. 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 **RATIFIED** by a full Committee at its next meeting taking place on 10 July **2012.**

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

Yours sincerely

[redacted]

/IPro ehaar
/ Chair: Biomedical Research Ethics Committee

health

Department:
Health
PROVINCE OF KWAZULU-NATAL

Health Research & Knowledge Management sub-component
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Tel.: 033 – 3953189
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Email.: hrkm@kznhealth.gov.za
www.kznhealth.gov.za

Reference : HRKM 29/12
Enquiries : Mr X Xaba
Tel : 033 – 395 2805

Dear Dr N. Madala

Subject: Approval of a Research Proposal

1. The research proposal titled **'Chronic kidney disease in KwaZulu Natal: Epidemiology, pathogenesis and outcome'** was reviewed by the KwaZulu-Natal Department of Health.

   The proposal is hereby **approved** for research to be undertaken at Addington and King Edward VIII Hospitals.

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
KwaZulu-Natal Department of Health
Date: 11/01/2012

PROFILE OF CKD IN KWAZULU-NATAL

DATA COLLECTION SHEET

Hospital: _____ Date.....1st renal clinic visit

I. Demographic data

Study ID no. _____ Patient Hospital no._____

Age (yrs): _____ Gender: Male μ Female μ

Occupation: Scholar Unemployed Employed **specify work_____**

Referral Source: _____ (name of hospital/ clinic)

Residence: _____

Cigarette smoking: Yes / No Alcohol use: Yes / No

II. Clinical data (History & examination)

History of CKD risk factors (circle where applicable):

Hypertension Type II diabetes Analgesic regular use **(specify ASA/NSAID)**

HIV SLE Other (specify) _____

Examination:

Weight _____ kgs Height _____ cms BMI _____

Waist circumference _____ cms Finger-prick glucose _____mmol/l

Systolic BP_____ mmHg Diastolic BP_____ mmHg (sitting)

Systolic BP_____ mmHg Diastolic BP_____ mmHg (erect)

Urine dipstick:

Proteinuria:	**nil**	**trace**	**1+**	**2+**	**3+**	**4+**
Haematuria:	**nil**	**trace**	**1+**	**2+**	**3+**	**4+**
Leucocyturia	**nil**	**trace**	**1+**	**2+**	**3+**	**4+**

Renal presenting problem:

CKD ESRD Nephrotic syndrome Acute nephritis ARF

CKD aetiology _____

III. Laboratory data

Blood

Serum creatinine _____ μmol/l Urea _____ mmol/l

Na _____ mmol/l K _____ mmol/l Chloride _____ mmol/l HC03 _____ mmol/l

Blood glucose _____ mmol/l Urates _____ mmol/l

Hgb _____ g/dl MCV _____ fl MCH _____ pg

Tot cholesterol _____ mmol/l Triglycerides _____ mmol/l LDL _____ HDL _____

Calcium _____ mmol/l Phosphate _____ mmol/l Alb _____g/l

Urine

Urine albumin/ creatinine ratio _____ Urine protein/ creatinine ratio _____

24-hr urine protein excretion rate _____ g/day

GFR

isotope GFR _____ ml/min normalized for area _____ ml/min

eGFR _____ ml/min or creat clearance _____ ml/min

Radiology

Kidney size (U/S or CT scan) Right _____ cm Left _____ cm

IV. Pharmacological data – Current treatment

Name or equivalent	**Daily dose**
Antihypertensives	
Enalapril	
Valsartan	
Hydrochlorothiazide	
Furosemide	
Amlodipine	
Prazosin	
Atenolol	
Hydralazine	
Other anti-HPTs: Methyldopa, Minoxidil, Spironolactone, etc.	
Atorvastatin	
Allopurinol	
OHAs	
Insulin	

Contact numbers:_____

alternate _____

CKD EPIDEMIOLOGY DATA COLLECTION SHEET

Hospital: _____ **Date** .....

I. Demographic data

1. Study ID no. _____ **2. Hospital no.**_____

3. Age (yrs): _____ **4.** Gender: Male =1 Female =2

5. Residence: _____ **6.** Referral Source: _____(name of hospital/ clinic)

7. Cigarette smoking: Yes=1 / No=0 **8.** Alcohol use: Yes=1 / No=0

9. Physical activity: None=3 <30min/day=2 30-60min/day=1 ≥60min/day=0

II. History

10. History of CKD risk factors: Is there a previous diagnosis of any 1 or more of the CKD risk factors listed below? Yes=1 / No=0
(If yes, circle appropriate answer below):

Hypertension Yes=1 / No=0 **Type II diabetes** Yes=1 / No=0 **Type I diabetes** Yes=1 / No=0

HIV Yes=1 / No=0 **HAART** Yes=1 / No=0 **SLE** Yes=1 / No=0

Analgesic daily use Yes=1/ No=0 (state Aspirin/ NSAID) _____

Tubulointerstitial disease Yes=1 / No=0,

If yes, specify type: **ADPKD (Polycystic kidney disease**=1 / **VUR (reflux)**=2 / **Chr pyelonephritis (CPN)**=3

Glomerulonephritis/GN Yes=1 / No=0, if yes specify cause: Unknown (Idiopathic)=1 / Known (HIV/ Hep B/ SLE/ Strep, etc)=2

Specify type of GN: MCNS=1 / Membranous=2 / FSGS=3 / MPGN=4 / DPGN=5 / Other=6 / Unknown=7

Other CKD risk factor (specify) _____

11. History of CVD: Is there previous diagnosis of any 1/more of the cardiovascular diseases listed below? Yes=1 / No=0
(If yes, circle appropriate answer below):

a) Dyslipidaemia b) Carotid disease/ CVA c) Ischaemic heart disease (angina) d) CCF e) Peripheral vascular disease (gangrene)

12. Pharmacological data – Current treatment

Name or equivalent	**Daily dose**
Antihypertensives	
ACEI [Enalapril (Pharmapress)/ Captopril (Capoten)**]**	
ARBs (Losartan/ Valsartan/ Telmisartan**)**	
Hydrochlorothiazide	
Furosemide	
Amlodipine (Novarsc/ Amloc**)**	
Prazosin	
Atenolol	
Hydralazine	
Other anti-HPTs: Methyldopa, Minoxidil, Spironolactone, **etc.**	
Atorvastatin (Lipitor)/ Simvastatin	
Allopurinol (Puricos)	
Oral Hypoglycaemic agents	
Insulin	

III. Examination

Measurements:

Weight _____ kgs Height _____ cms BMI _____ kg/m^2

Waist circumference _____ cms Finger-prick glucose _____ mmol/l

Systolic BP_____ mmHg Diastolic BP_____ mmHg (sitting)

Systolic BP_____ mmHg Diastolic BP_____ mmHg (erect)

Urine dipstick:

Proteinuria:	**nil**	**trace**	**1+**	**2+**	**3+**	**4+**
Haematuria:	**nil**	**trace**	**1+**	**2+**	**3+**	**4+**
Leucocyturia	**nil**	**trace**	**1+**	**2+**	**3+**	**4+**

IV. Routine laboratory tests

Blood:

Serum creatinine _____ μmol/l Urea _____ mmol/l eGFR _____ ml/min

Na _____ mmol/l K _____ mmol/l Chloride _____ mmol/l HC03 _____ mmol/l

Urates _____ mmol/l Bld glucose _____ mmol/l ***If diabetic***, HbA1c_____ %

Hgb _____ g/dl MCV _____ fl MCH _____ pg C-reactive protein_____ U/l

Tot cholesterol _____ mmol/l Triglycerides _____ mmol/l LDL _____ mmol/l HDL _____ mmol/l

Calcium _____ mmol/l Phosphate _____ mmol/l Alb _____ g/l

Urine:

Urine albumin/ creatinine ratio _____ **OR** Urine protein/ creatinine ratio _____

V. Radiology (if available)

Kidney Ultrasound:

Normal (10-12 cm) Bordeline (9-9.9 cm) Large (>12 cm) Small (<9 cm)

Right _____ cm Left _____ cm

Dexa scan:

Body Fat % _____

VI. Glomerular filtration rate (GFR)

Radioisotope GFR **(GFR subjects only)** _____ ml/min normalized for area _____ ml/min

MDRD eGFR _____ml/min CKD-EPI eGFR _____ ml/min CG eGFR _____ ml/min

VII. Specialized laboratory tests (1 red top, 2 purple top for research study purposes only)

Cystatin C (GFR subjects only) _____ Beta trace protein (GFR subjects only) _____

Interleukin 6 (subjects & controls) _____ Interleukin 18 _____

DIVISION OF INTERNAL MEDICINE
Nelson R Mandela School of Medicine
College of Health Sciences

CHRONIC KIDNEY DISEASE STUDY

DATA SHEET FOR DEXA SCAN

1. Name: .....
2. Study No.: .....
3. Hospital No.: .....

4. Have you had any X-rays in the past ten (10) days? Yes ☐ No ☐

If Yes, which body areas were X-rayed? .....

.....

5. Have you had a GFR test done at Medical Physics GFR? Yes ☐ No ☐

If Yes, when? (give an approximation, e.g. 2 months ago/Jan) .....
(if recent, re-schedule DEXA appointment to 2 weeks after GFR)

6. Have you been injected with other dye, barium or radioactive material?
Yes ☐ No ☐
(if Yes, re-schedule DEXA appointment to 2 weeks after GFR)

7. Height ..... m Weight ..... kg
8. Menopause Yes ☐ If yes, when? (give approximation).....
No ☐ If no, give LMP date: .....

Thank you for participating.

Dr N. Madala/ Sr N. Zungu

UNIVERSITY OF
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06 June 2017

Dr N D Madala
Department of Nephrology
Nelson R Mandela School of Medicine
University of KwaZulu-Natal

Dear Dr Madala

PROTOCOL: Chronic Kidney Disease in KwaZulu-Natal: Epidemiology, Pathogenesis and outcome. REF: BE179/11

NEW TITLE OF PROTOCOL: Epidemiology of Chronic Kidney Disease in KwaZulu-Natal: Risk Factors, Complications and diagnostic methods.

Your correspondence received on 18 May 2017 submitting an application for Amendments to change the title as above has been **noted and approved** by a sub-committee of the Biomedical Research Ethics Committee.

This approval will be **ratified** at the next BREC meeting to be held on **09 July 2017**.

Yours sincerely

[redacted]
Mrs A Marimuthu
Senior Administrator: Biomedical Research Ethics