PERFORMANCE OF THE COCKCROFT-GAULT AND MODIFICATION OF DIET IN RENAL DISEASE EQUATIONS COMPARED TO 24 HOUR CREATININE CLEARANCE IN AFRICANS WITH CHRONIC KIDNEY DISEASE AT KENYATTA NATIONAL HOSPITAL

A dissertation submitted in part fulfilment of the requirements for the degree of master of medicine in Internal Medicine

By

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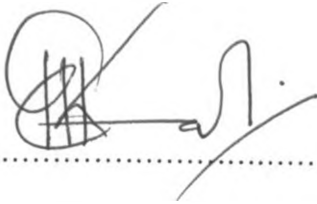University of Nairobi.

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DECLARATION

THIS STUDY WAS CARRIED OUT AS PART OF FULFILMENT OF THE DEGREE OF MASTERS IN MEDICINE, INTERNAL MEDICINE.

I CERTIFY THAT THIS DISSERTATION IS MY OWN ORIGINAL WORK AND HAS NOT BEEN SUBMITTED FOR A DEGREE AT ANY OTHER UNIVERSITY.

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ABBREVIATIONS

AASK : African American Study on Hypertensive and Kidney disease

Alb : Albumin

ARF : Acute renal failure

BUN : Blood Urea Nitrogen

C-G : Cockcroft-gault formular

cC-G : Corrected Cockcroft-Gault

CKD : Chronic kidney disease

Cr : Creatinine

Crcl : Creatinine clearance

CVD : Cardiovascular disease

Cx : Urinary clearance of an ideal filtration marker

DTPA : Diethylenetetrapantaacetic acid

EDTA : Ethylenediaminetetraacetic acid

eqn : Equation

ESRD : End-stage renal disease

GFR : Glomerular filtration rate

KDIGO: Kidney Disease Improving Global Outcomes

K/DOQI: Kidney disease outcomes quality initiative

NKF : National Kidney Foundation

KNH : Kenyatta National Hospital

MDRD: Modification of diet in renal disease

MDRD4: abbreviated Modification of Diet In Renal Disease Equation(4 variables included)

MDRD7: original Modification of Diet In Renal Disease Equation(6 variables included)

NIH : National Institute of Health

NPV : Negative predictive value

PPV : Positive predictive value

Px : Serum concentration of a filtration marker

R^2 : Precision (as derived from regression curves)

Scr : serum creatinine

Ucr : urine creatinine

Ux : concentration of a given filtration marker excreted in urine

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ABSTRACT

2.1 Background

The worldwide rise in the number of patients with chronic kidney disease and end-stage renal failure is threatening to reach epidemic proportions over the next decade. The Glomerular Filtration Rate (GFR) is traditionally considered the best overall index of kidney function in health and disease. Early detection of Chronic kidney disease (CKD) requires identification of individuals with reduced GFR.GFR has been estimated by measurement of Serum creatinine and creatinine excretion in a 24-h urine sample and computation of creatinine clearance. More than 25 different formulas have been derived for estimating GFR using plasma creatinine corrected for a combination of factors like gender, body size, race and age. The most widely used GFR prediction equations for adults are those proposed by Cockcroft and Gault and Modification of Diet in Renal disease equations i.e MDRD original study equation and more recently the MDRD abbreviated equation. These three equations have been validated in heterogeneous populations with various stages of CKD where they have demonstrated greater accuracy and consistency in estimating GFR by incorporating other known demographic and clinical variables other than serum creatinine alone.

2.2 Objectives

To determine the performance of the Cockcroft-Gault and Modification Of Diet in Renal Disease equations(MDRDoriginal and MDRDabbreviated) compared to the 24 hour Creatinine Clearance in Africans with chronic kidney disease at Kenyatta National Hospital.

2.3 Methods

A cross-sectional analysis of the measured 24hr creatinine clearance and estimated GFR using MDRDoriginal, MDRDabbreviated and Cockcroft-Gault equations was carried out on 115 native Africans with CKD to assess the performance of these three commonly used formulas.Data collected included demographic variables,history of hypertension,history of diabetes,and serum biochemistry indices.Data was analysed using SPSS version 12.0

2.4   Outcome Measures

Outcome measures included determining the GFR of the study population as calculated by Cockcroft-Gault equation and MDRD equation 7(original equation) and abbreviated MDRD equation(equation 4) GFR estimating equations, comparing them with the 24 hour creatinine clearance. Indicators of the performances of these equations were derived from precision, bias and accuracy calculating equations.

2.5   Results

Comparison was made between 24 hour creatinine clearance, Cockcroft & Gault and MDRD prediction equations on 115 African adult patients with CKD aged between 18 and 87 years old. Their mean age was 48.1 years. Sixty-four males (55.7%) and 51 female (44.3%) subjects were studied. Thirty-nine (33.9%) were hypertensive patients,6 (5.2%) had diabetes, 36 (31.3%) had diabetes with hypertension and 34 patients (29.6%) were neither hypertensives nor diabetics. MDRD original equation had better correlation with 24 hour creatinine clearance as compared with Cockcroft-Gault and MDRD abbreviated equations. Statistical correlation was r = 0.815 for MDRDoriginal equation, r =0.794 for MDRD4 equations and r = 0.781 for Cockcroft-Gault equation .MDRD abbreviated equation had the least bias compared to MDRD original and Cockcroft-Gault equations. The accuracy was greatest using MDRD original equation with 78.3% of calculated GFR values falling within 30% and 93% being within 50% of the measured 24hr creatinine clearance.

2.6   Conclusion

The 3 GFR estimating equations MDRD original equation, MDRD abbreviated and Cockcroft-Gault formulae had good agreement with the measured 24 hour creatinine clearance in stage 3, 4 and 5 of Chronic Kidney Disease. This means that the values of GFR as measured by creatinine clearance that classifies patients into stage 3, 4 and 5 of CKD will be in agreement with GFR values as calculated using the 3 GFR estimating equations in that they will also classify these same patients into CKD stage 3, 4 and 5.Patients with CKD stages 1 and 2 were not studied.

LITERATURE REVIEW

3.1 Introduction

The worldwide rise in the number of patients with chronic kidney disease and end-stage renal failure is threatening to reach epidemic proportions over the next decade. The GFR is traditionally considered the best overall index of kidney function in health and disease. Early detection of CKD requires identification of individuals with reduced GFR[1].GFR has been estimated by measurement of Scr and creatinine excretion in a 24-h urine sample and computation of creatinine clearance. More than 25 different formulas have been derived for estimating GFR using plasma creatinine corrected for a combination of factors like gender, body size, race and age. The most widely used GFR prediction equations for adults are those proposed by Cockcroft and Gault and Modification of Diet in Renal disease equations i.e MDRD original study equation and more recently the MDRDabbreviated equation.

3.2 Epidemiology

The worldwide rise in the number of patients with CKD is reflected in the increasing number of people with ESRD treated by renal replacement therapy—dialysis or transplantation.[2] In the UK, the annual incidence of ESRD has doubled over the past decade to reach about 100 new patients per million of population,[3] well below the European average (about 135 per million) and rates in the USA. The UK trend, like trends in other more developed countries, is expected to continue to rise at an annual rate of around 5–8%.Two factors are important. The first is the ageing of the population; the incidence of ESRD is higher in elderly people than in the general population (the annual incidence in people older than 65 years in the USA is more than 1200 per million[4]. The second factor is the global epidemic of type 2 diabetes mellitus; the number of people with diabetes worldwide (currently about 154 million) is predicted to double within the next 20 years. This increase will be most notable in less developed countries, where the number of diabetic patients could rise from 99 million to 286 million by 2025, with an expected parallel epidemic of diabetic nephropathy.[5]

About 90% of treated ESRD patients come from more developed countries that can still afford the cost of renal replacement therapy.[6] In the USA, the annual expenditure on ESRD is estimated to increase to more than US$28 billion by 2010.[4] In Europe, dialysis alone takes up about 2% of

health-care budgets with only a small proportion (<0·1%) of the population needing treatment. There is a clear and direct relation between the gross national product and the availability of renal replacement therapy, with less developed countries unable to meet the increasing demand.[6] The huge disparity in the prevalence of ESRD between the more and less developed countries probably stems from the inadequacy of health-care resource allocation to programmes of renal replacement therapy. However, disparities in the incidence of ESRD within and between more developed countries are likely to reflect the racial and ethnic mix. For example, in the USA and Australia the annual incidence of ESRD is substantially lower in white than in African-American or aboriginal people.[4,7]

The number of patients with ESRD probably underestimates the entire burden of CKD because the numbers with earlier stages of disease (stages 1 to 4,) are likely to exceed by as much as 50 times those reaching ESRD (stage 5).[8] For instance in the USA, data derived from the third National Health and Nutrition Examination Survey have implied that up to 11% of the general adult population (19 million) could have some degree of CKD, including more than 8 million individuals with glomerular filtration rates of less than 60 mL per min· This analysis also estimated that 5·9 million people could have stage 1 CKD with normal renal function.[8] However, these observations have substantial limitations, including the basing of prevalence estimation on single serum creatinine measurements, which are subject to variations owing to differences in calibration systems between laboratories.[9] Subsequently, the estimates based on serum creatinine were converted into estimates based on glomerular filtration rate by use of the formula of the Modification of Diet in Renal Diseases study, which has not been fully validated in different populations and at different stages of CKD. In addition, age-related decline in glomerular filtration rate, affecting up to 40% of people aged over 65 years, could have led to overestimation of the actual burden of CKD because many of these people have impaired but stable kidney function. [10, 11]

3.3   Assessment of Kidney Function

Patients with kidney disease may have a variety of different clinical presentations. Some have symptoms that are directly referable to the kidney (gross hematuria, flank pain) or to extrarenal symptoms (edema, hypertension, signs of uremia). Many patients, however, are asymptomatic and are noted on routine examination to have an elevated serum creatinine concentration or an abnormal urinalysis.

Once kidney disease is discovered, the presence or degree of kidney dysfunction and rapidity of progression are assessed, and the underlying disorder is diagnosed. Although the history and physical examination can be helpful, the most useful information is initially obtained from estimation of the glomerular filtration rate (GFR) and examination of the urinary sediment.

Estimation of the glomerular filtration rate (GFR) is used clinically to assess the degree of kidney impairment and to follow the course of the disease. However, the GFR provides no information on the cause of the kidney disease. This is achieved by the urinalysis, measurement of urinary protein excretion, and, if necessary, radiologic studies and/or kidney biopsy.[11]

3.4 Evaluation Of The Glomerular Filtration Rate

3.4.1 Overview

The GFR is equal to the sum of the filtration rates in all of the functioning nephrons; thus, the GFR gives a rough measure of the number of functioning nephrons. The filtering units of the kidney, the glomeruli, filter approximately 180 liters per day (125 mL/min) of plasma. The normal value for GFR depends on age, sex, and body size, and is approximately 130 and 120 mL/min/1.73 m2 for men and women, respectively, with considerable variation even among normal individuals. A reduction in GFR implies either progression of the underlying disease or the development of a superimposed and often reversible problem, such as decreased renal perfusion due to volume depletion. There is not an exact correlation between the loss of kidney mass and the loss of kidney function. Since the kidney adapts to loss in function by compensatory hyperfiltration and/or increasing solute and water reabsorption in the remaining normal nephrons, an individual with the loss of one-half of total kidney mass does not necessarily have one-half the amount of normal kidney function. Therefore a stable GFR does not necessarily imply stable disease. Similarly, an increase in GFR may indicate improvement in the kidney disease or may imply an increase in filtration (hyperfiltration) due to hemodynamic factors.[12]

3.4.2 Measurement

GFR cannot be measured directly, but could be estimated from the urinary clearance of an ideal filtration marker.

Equation 1: $C_x = (U_x \times V)/P_x$

where C_x is clearance, P_x is the serum concentration of the marker, U_x is the urinary concentration of x and V is the urine flow rate.

An ideal filtration marker is defined as a solute that is freely filtered at the glomerulus, nontoxic, neither secreted nor reabsorbed by the kidney tubules, and not changed during its excretion by the kidney. If these criteria are met, filtered load is equal to the rate of urinary excretion:

Equation 2: $GFR \times Px = (Ux \times V)$

Where GFR X Px is the filtered load, and Ux X V is the urinary excretion rate. By substitution into Equation 1:

Equation 3: $GFR = Cx$

The gold standard of exogenous filtration markers is inulin. Inulin is a physiologically inert substance that is freely filtered at the glomerulus, and is neither secreted, reabsorbed, synthesized, nor metabolized by the kidney. Thus, the amount of inulin filtered at the glomerulus is equal to the amount excreted in the urine, which can be measured. Inulin, however, is in short supply, expensive, and difficult to assay. Furthermore, the classic protocol for measuring inulin clearance requires a continuous intravenous infusion, multiple blood samples, and bladder catheterization.[14]

Various less cumbersome methods for measuring clearance are available: using alternative filtration markers (such as radioactive or nonradioactive iothalamate, iohexol, DTPA, or EDTA), bolus administration of the marker (subcutaneous or intravenous), spontaneous bladder emptying, and plasma clearance. While these methods are simpler, all have disadvantages that limit their application in clinical practice and affect the interpretation of research studies.[14,15]

3.4.3   Estimation

In the United States, the most common methods utilized to estimate the GFR are the serum creatinine concentration, the creatinine clearance, or estimation equations based upon the serum creatinine: such as the Cockcroft-Gault equation and Modification of Diet in Renal Disease (MDRD) Study equations. The abbreviated MDRD Study equation, in particular, is being increasingly utilized. In 2002, the National Kidney Foundation (NKF) revised its practice guidelines for CKD and now recommends the use of a four-variable modification of diet in renal disease (MDRD) equation (MDRD4 equation) or the Cockcroft–Gault equation for creatinine clearance (CL_{cr}) to estimate the glomerular filtration rate (GFR) and better detect early-onset CKD.[1,2] These guidelines further recommend that clinical laboratories estimate the GFR using an equation designed to estimate or predict the GFR based on available patient data, such as age, sex, weight, and serum creatinine, whenever reporting a serum creatinine measurement.[1,16]

3.5. Background:

3.6 COCKCROFT AND GAULT FORMULAR

The Cockcroft-Gault equation was first published in 1976 and has been the subject of multiple validation studies with literature indicating over 50 published articles .The equation estimates creatinine clearance (Crcl) and is based on the daily urine creatinine excretion given the age, weight and sex of the patient.[13] i.e

Crcl = 1.23 x (140 - age) x body weight(kg)

(ml/min)   Scr in umol/L   (substitute 1.23 with 1.04 in female)

Between 1989 and 1997, several articles reported results from the MDRD study funded by the National Institutes of Health (NIH).[3-6] This multicenter,controlled trial of 1628 patients compared the effects of strict blood pressure control and dietary protein restriction (low-protein diet, 0.58 g/kg; very-low-protein diet, 0.28 g/kg) with a more typical protein diet (1.3 g/kg) to determine the progression of CKD. Lower-protein diets did not significantly affect the progression of CKD over the mean 2.2-year study.[3-5,7,8]

However, study results did demonstrate a nonsignificant (p = 0.07) trend of a slower decline in the GFR in the group receiving the very-low- protein diet. This MDRD study group later formed the basis of the MDRD GFR study group.

3.7   Findings of The MDRD GFR Study

Multiple stepwise linear regression of log-transformed values was conducted on demographic and laboratory data from 1070 patients randomly selected from the original study population (i.e., the training sample). Seven independent factors were associated with a significantly lower GFR ($p < 0.001$): higher serum creatinine levels, older age, female sex, nonblack ethnicity, high blood urea nitrogen (BUN) level, lower serum albumin level, and lower urine urea nitrogen excretion (UUN) level. Baseline variables that were not independent predictors of the GFR included weight, height, diagnosis of diabetes, serum phosphorus and calcium levels, mean arterial blood pressure, and urine creatinine and urine phosphorus levels. From these data, two slightly different six-variable equations were developed to predict the GFR, one that uses UUN

$$GFR = 198(Cr^{-0.858} \times age^{-0.167}) \times BUN^{-0.293} \times UUN^{-0.294} \times$$

$$(1.178 \text{ if black}) \times (0.822 \text{ if female})$$

and one that uses serum albumin

$$GFR = 170(Cr^{-0.999} \times age^{-0.176}) \times BUN^{-0.170} \times albumin^{-0.318} \times$$

$$(1.178 \text{ if black}) \times (0.822 \text{ if female})$$

Of these six variables, serum creatinine was determined to have the greatest impact on predicting GFRs in both of these equations. It is interesting to note that the regression analysis was performed on log-transformed values that were fit to an exponential (geometric) model and then reexpressed as a multiplicative linear relationship. The regression coefficients determined in this training sample were then applied to a separate validation sample of 558 patients to evaluate the performance of each prediction equation. To maximize the accuracy of these prediction equations, the training sample's predictive coefficients were reapplied to all 1628 patients to form the basis of the final MDRD equations. Correlations were performed for both six-variable equations, 24-hour urine Crcl, and Cockcroft–Gault Crcl versus a gold standard measured GFR based on renal clearance of ^{125}I-iothalamate. The 24-hour urine Crcl and Cockcroft–Gault Crcl were expressed (i.e., normalized) to 1.73 m^2 BSA. The median absolute error provides an indication of the amount of overestimation of the GFR for each prediction equation. For example, the Cockcroft– Gault Crcl equation overestimated the GFR in this comparison by 16%. The six-variable regression equation that included UUN explained 91.2% (r^2, 0.9123) of the variance between MDRD-estimated GFRs and measured GFRs .The six-variable equation that substitutes albumin for UUN yielded an r^2 of 0.903. Serum creatinine accounted for 80% of the variability in GFRs in these regression analyses. The major result of this study was the recommendation to use an MDRD equation to estimate GFRs, which yields a lower GFR than that produced with other common equations that estimate Crcl. [19,22-24]

3.8 MDRD4 Equation

In 2000, Levey et al. [14] published the MDRD4 equation, which uses age, sex, ethnicity, and serum creatinine to predict the GFR:

$$GFR = 186\,(Cr^{-1.154} \times age^{-0.203}) \times (1.212 \text{ if black}) \times (0.742 \text{ if female})$$

This simplified formula was derived from a reanalysis of the variables from the same 1628 patients, excluding UUN, albumin, and BUN from these equations, and is recommended by the 2002 NKF practice guidelines for routine GFR estimation.[1]

3.9 Summary of NKF Practice Guidelines

In February 2002, the Kidney Disease Outcomes Quality Initiative (K/DOQI) work group published 15 CKD practice guidelines to provide clear definitions of the stages of CKD and to make numerous evidence-based recommendations for earlier detection of CKD.[1] This group recognizes that the GFR is the best measure of overall kidney function, noting that the normal GFR varies by the patient's sex, age, and body size. A GFR of <60 mL/min/1.73 m^2 represents loss of ≥50% of kidney function in adults, resulting in an increased rate of CKD complications. This is important because the K/DOQI work group identified two principal outcomes of CKD: the progressive loss of kidney function over time and the development and progression of cardiovascular disease (CVD). A decreased GFR is associated with numerous complications, including hypertension, anemia, malnutrition, bone disease, neuropathy, and decreased quality of life. All can be prevented or ameliorated by earlier treatment of CKD. Cardiovascular events are more common in patients with CKD. [12,14,15] CKD appears to be a risk factor for CVD, and CVD in patients with CKD is treatable and potentially preventable. Specific NKF practice guidelines recommend use of the MDRD4 equation to predict GFR. The K/DOQI work group concluded that an equation that estimates the GFR within 30% of a measured value (i.e., renal clearance of inulin or ^{125}I-iothalamate) is acceptable for use as a screening and monitoring tool to detect CKD, defined as a GFR of <60 mL/min/1.73 m^2. For example, a patient with a measured GFR of 60 mL/min/1.73 m^2 would have an estimated GFR of 42–78 mL/min/1.73 m^2 The K/DOQI guidelines classified patients by chronic kidney disease (CKD) stage, which is defined in part by the estimated GFR. The GFR should be estimated from the MDRD and Cockcroft-Gault equations, which take into account the serum creatinine concentration and some or all of the following variables: age, gender, race, and body size. [16, 17]

Creatinine clearance — Creatinine is derived from the metabolism of creatine in skeletal muscle and from dietary meat intake; it is released into the circulation at a relatively constant rate and has a stable plasma concentration. Creatinine is freely filtered across the glomerulus and is neither reabsorbed nor metabolized by the kidney. However, approximately 10 to 40 percent of

urinary creatinine is derived from tubular secretion by the organic cation secretory pathways in the proximal tubule. [16]

If the effect of secretion is ignored, then all of the filtered creatinine (equal to the product of the GFR and the serum creatinine concentration [SCr]) will be excreted (equal to product of the urine creatinine concentration [UCr] and the urine flow rate). Thus:

$$GFR \times SCr = UCr \times V$$

$$GFR = [UCr \times V]/SCr$$

This formula is called the creatinine clearance and tends to exceed the true GFR by the 10 to >20 percent of urinary creatinine that is derived from tubular secretion. [17] This error is balanced by an opposing error of almost equal magnitude in the measurement of the serum creatinine. National standardization of serum creatinine assays to creatinine reference materials, which are expected to come into effect by 2008, will abolish this error. CrCl measurements will then be consistently 10 to 15 percent higher than GFR. The creatinine clearance is usually determined from a 24 hour urine collection, since shorter collections tends to give less accurate results.

Estimation equations — GFR estimating equations improve upon the serum creatinine alone by incorporating known demographic and clinical variables as observed surrogates for the unmeasured physiological factors other than GFR that affect serum creatinine concentration.

Estimation equations also appear to be reasonably accurate for following changes in GFR over time. [16,17,]

The most common equations used in the United States are the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) study equations. The MDRD study equation is increasingly utilized in the United States.

As for serum creatinine, proper interpretation of the results from these formulas requires stable kidney function. [20]

4.0   Evaluation of the equation in other populations

The MDRD Study equation was derived from primarily white subjects who had non-diabetic kidney disease, with mean GFR of 40 mL/min per 1.73 m2. Subsequently, there has been extensive evaluation of the performance of the equation in other populations including African Americans, Europeans, and Asians with non-diabetic kidney disease, diabetic patients with and

without kidney disease, patients with liver disease, kidney transplant recipients, and potential kidney donors. [21-41]

Poggio *et al* and colleagues studied the performance of the MDRD & Cockcroft-Gault. equations and analyzed them in patients with CKD and in potential kidney donors. In patients with GFR < 60 ml/min per $1.73m^2$, the MDRD equation performed better than Cockcroft-Gault formula but equations underestimated measured GFR in the kidney donor group. This data added further validation of MDRD equation in outpatients with moderate to advanced kidney disease as well as those with diabetic nephropathy. [37]

Lewis J *et al* and co-workers did a comparison of cross-sectional renal function measurements in African Americans with hypertensive nephrosclerosis and of primary formulas to estimate GFR. Data in this study were also used to derive a new five-term formula for estimating GFR that was slightly more accurate in African American Study on Hypertensive and Kidney disease(AASK) study than the MDRD formula (median percentage error,12.4% for the MDRD formula Vs 12.1% for the AASK formula).

They concluded that important features exist in renal variables between African Americans and non-African Americans and between African American men and African American women. [38]

Jafer *et al* performed a population based cross-sectional study on 262 individuals and compared a derived prediction formula with the MDRD & Cockcroft-Gault equations. They concluded that inclusion of terms for ethnic and racial groups other than white and black might improve performance of GFR estimating equations. [57]

Aizawa *et al* and colleagues evaluated the correlation between creatinine clearance(Crcl) derived from a 24hr urinary collections and predicted Crcl or GFR calculated by the c-gault equation,Horio and MDRD equations. These formulae demonstrated a strong correlation and concluded that these predictive formula could be useful for the prediction of creatinine clearance in Japanese patients. [58]

Mcligeyo compared 24h crcl with several GFR predicting equations i.e Hull,Jellife,Gates and Cockcroft-Gault equations.He reported good correlation between 24h Crcl and Cockcroft-G equation. [59]

The predictive accuracy of the Cockroft and Gault equation in the assessment of creatinine clearance was evaluated in 30 Nigerian patients with hypertension, congestive heart failure, chronic renal failure and varying degrees of renal impairment. There was a high correlation between the measured and predicted creatinine clearance as shown by the regression equation, Ajayi *et al.* [60]

Work done by Adnan *et al* comparison was made between conventional creatinine clearance and Cockcroft & Gault and Modification of Diet in Renal Disease (MDRD) prediction equations on 369 cases which revealed strong correlation with conventional creatinine clearance, MDRD equation has better correlation as compared with Cockcroft- Gault creatinine clearance .[61]

Another study by Le Rich *et al* assessed patients in CKD stages 1-5.Cockcroft-Gault correlated better with 24h creatinine clearance compared to MDRD abbreviated equation in estimating GFR of the study subjects .[62]

Almond *et al* studied patients with serum creatinine > 200umol/L and found that MDRD4 was superior to cockcroft-gault in predicting 24h creatinine clearance of < 15 ml/min .[63]

Garcia-Neiro *et al* studied 615 adults >18yrs with advanced and preterminal CKD and demonstrated acceptable agreement of MDRD4 and 24h Crcl in advanced stages of CKD .[64]

Work done by Shoker *et al* demonstrated limited accuracy of the original Cockcroft-Gault to predict creatinine clearance particularly in patients with crcl below 50ml/min with an overall accuracy in less than 1/3 of the calculated within 30% range from the measured. However correction for body surface area demonstrated more accuracy .[65]

5.0   RESEARCH QUESTION

Are the performances of MDRD, Cockcroft-Gault equations and the 24hour creatinine clearance comparable in predicting the GFR of black Africans with CKD?

5.1   STUDY   JUSTIFICATION

Chronic kidney disease (CKD) is a growing global challenge. Early detection plus aggressive primary and secondary prevention are the best options for developing countries to adopt as CKD is associated with cardiovascular and non- CVD related morbidities and fatal outcomes. Such economies including Kenya cannot meet the ever increasing demands for renal replacement therapy. So there is need to develop new screening tools for early detection of CKD so as to classify, stratify and plan management as this will decrease rate of progression to ESRD if appropriate treatment is instituted early.

Methods currently in use have been extrapolated or adopted from other populations without validating such tools. This can lead to misclassification of stage of CKD and subsequent unnecessary early or late renal replacement interventions and or excessive monitoring, referrals to nephrologists and related costs.

The MDRD and Cockcroft-Gault equations have been used in many populations including African Americans who have different body & muscle composition, diet and lifestyle hence a potential source of variability and error if these equations are applied in native Africans. There are no studies done in Kenya that has assessed MDRD equations.
The Kidney Disease Improving Global outcomes(KDIGO) group and the Kidney Disease Outcomes Quality initiative(KDOQI) group recommend that these equations be validated in populations that are non-US cohorts as they cannot be generalized.

Determining creatinine clearance, or GFR is necessary in pharmaceutics and drug –dosing adjustments in patients with CKD to ensure appropriate dosing and prevention of potential renal toxicity in this group of patients.

Application of GFR estimating equations is convenient in routine clinical practice compared to 24 hour urine collection which is time consuming and subject to errors.

6.0   BROAD OBJECTIVE

6.1   Primary objective:

To determine the performance of the Cockcroft-Gault, Modification of Diet in renal disease equations compared to 24hour creatinine clearance over a range of CKD stages.

6.2   SPECIFIC OBJECTIVES:

1. To determine the 24hr creatinine clearance of patients with CKD.
2. To determine the estimated GFR using the Cockcroft-Gault, MDRD (original) and MDRD (abbreviated) equations in patients with CKD.
3. To correlate the measured creatinine clearance with the Cockcroft-Gault and MDRD (original) and MDRD (abbreviated) equations.
4. To determine the bias, precision and accuracy of the three equations as described by the percentage of their GFR values falling within 30 or 50% (above or below) the measured creatinine clearance.

7.0   MATERIALS AND METHODS

7.1   Study Design

A cross-sectional study

7.2   Study Area

Kenyatta National Hospital medical wards, renal and diabetic clinics.

7.3   Study Population

All patients attending clinic with CKD aged 18yrs and above.

7.4   Patient Selection

7.4.1. Inclusion criteria

Adult patients with chronic kidney disease admitted in medical wards and those attending the renal or diabetic clinics.

7.4.2   Exclusion criteria

- All patients who declined consent.
- Patients with acute renal failure.
- Patients with malnutrition, amputation, heart failure and severe muscle wasting.
- Patients who are taking Cimetidine or Trimethoprim or who are on any form of renal replacement therapy.

7.5   Case definition

CKD is kidney damage for **> or = 3** months, as defined by structural and functional abnormalities i.e a renal ultrasound demonstrating contracted kidneys and a serum creatinine of **> 200umol/L**. Measured GFR will be derived from calculating the creatinine clearance i.e

$$\textbf{GFR} = [\ \underline{UCr\ x}\ V\ ]/\textbf{Scr} \quad \text{i.e 24hr creatitine clearance.}$$

V = urinary flow rate (volume of urine in 24hrs);

Ucr = urine creatinine concentration

Scr = serum creatinine concentration

Estimated GFR will be calculated by using three equations:

a) corrected Cockcroft-Gault(cCG) equation

$$CrCl = \frac{1.23 \times (140-age) \times body\ weight(kg) \times 1.73/BSA}{Scr\ in\ umol/L}$$

(ml/min)

(Substitute 1.23 with 1.04 in female subjects)

b) Modification of Diet in Renal disease equation(MDRD) –original eqn:

$$GFR = 170 \times (Scr)^{[-0.999]} \times (Age)^{[-0.176]} \times (BUN)^{[-0.170]} \times (Alb)^{[+0.318]}$$
$$\times (0.762\ if\ Female) \times (1.18\ if\ black)$$

c) Modification of Diet in Renal disease equation 4 (MDRD 4)

$$GFR = 186(Scr^{[-1.154]} \times age^{[-0.203]}) \times (1.212\ if\ black) \times (0.742\ if\ female)$$

24 hour creatinine clearance = $\dfrac{UCr \times V \times 1.73/BSA}{Scr \times 1440}$

Corrected for BSA

(ml/min/1.73m^2)

BSA = square root of [Height(cm) x weight(kg)/3600]

Where Ucr = urine creatinine

Scr = serum creatinine

BSA = body surface area

Bias = $\dfrac{1}{N-1} \Sigma(pe\ i)$

Where *pe i* is the predicted value - the true value.

Precision : the value of R^2 from the linear regression of measured CrCl on estimated GFR .It expresses the variability (or dispersion) of a prediction equation estimates around the measured creatinine clearance.

Accuracy : [predicted value – true (i.e 24hr Crcl measurement)] x100/Crcl

Relative accuracy : the percentage of estimates falling within 30% and 50% of measured 24 hour Crcl.e.g if 99% of the time an estimation equation yields an estimate within 10% of the measured creatinine clearance,it would be a very accurate and useful clinical tool.[69,70]

7.6 Stages of CKD according to the US National Kidney Foundation and the Kidney Disease Outcomes Quality Initiative

Stage 1

Kidney damage (pathological abnormalities or markers of damage including abnormalities in blood or urine tests or in imaging studies) with normal or raised glomerular filtration rate ($\geq$90 mL per min per 1·73 m^2)

Stage 2

Glomerular filtration rate 60–89 mL per min per 1·73 m^2 with evidence of kidney damage

Stage 3

Glomerular filtration rate 30–59 mL per min per 1·73 m^2

Stage 4

Glomerular filtration rate 15–29 mL per min per 1·73 m^2

Stage 5

End-stage renal failure; glomerular filtration rate <15 mL per min per 1·73 m^2

National Kidney Foundation practice guidelines [17]

7.7 Data collection

The patients with CKD were identified from patient's file by the principal investigator and/or his assistant before the clinics started. The patients were introduced to the study and their eligibility assessed. Once eligibility criteria had been fulfilled, signed consent was obtained and a targeted history and physical examination performed. The study questionnaire was then administered. Those who did not have their recent renal function tests had them done the same day. The patients were then instructed on how to do a 24 hr urine collection.

In order to ensure that the maximum number of patients return with the collected urine transport allowance was provided to those with financial limitations. Patients with CKD and admitted in medical wards and eligible for the study were also recruited following a written/signed consent.

The 24 hr urine plus 2ml heparinized blood sample were submitted to the renal laboratory and their creatinine clearance (measured GFR) and the corrected Cockcroft-Gault and MDRD formulas calculated (estimated GFR).

7.8 Sampling

Consecutive sampling technique was done till the required sample size of 115 patients was achieved.

7.9   Sample Size estimation.

The sample size is calculated using the following method [68]

$$N = (n+v)^2 \; \frac{p1(1-p1)+p2(1-p2)}{(p1-p2)^2}$$

where n= sample size

　　u=B at 95%, 1.64 (power of study)

　　v= a = 0.05 = 1.96(standard normal at 95% confidence interval)

　　p1= accuracy of test 1=0.85

　　p2=accuracy of test 2= 0.65

The minimum sample size shall be **115 patients**

7.10   Laboratory Methods

Venous blood was aseptically collected in yellow top, gel separator BD Vacutainer. After separation of serum, the serum creatinine was estimated by alkaline picrate, rate kinetic method using thermo-infinity creatinine liquid stable reagent TR 35121 Technical RA 1000 semiautomated clinical chemistry analyzer. Twenty- four hour urine was collected in containers with 10cc of conc HCl acid preservative. Volume of the urine passed in 24 hours was measured in milliliters in volumetric flasks. After thorough mixing of urine sample, 1:10 dilutions were prepared manually with deionized water. The diluted urine samples were also analyzed by alkaline picrate, rate kinetic method using thermo-infinity creatinine liquid stable reagent TR 35121 TechnicalRA 1000 semiautomated clinical chemistry analyzer and the results were multiplied by 11 to get creatinine concentration in urine samples.

Internal quality control was performed 3 times a day in the renal lab on a daily basis to ensure that the precision of the results obtained is maintained.

7.11   Data Management

Data entry and statistical analysis was done using the Statistical Package for Social science (SPSS) version 12.Data validation will be carried out before analysis.

Continuous data such as age, height, weight, BSA, body mass index, serum creatinine, serum urea, serum albumin and measured GFR were described using means, standard deviations, medians, proportions and frequency distribution while categorical data were analyzed using

percentages and their corresponding confidence interval. Association was examined using chi-square test for categorical data and a P value of <0.05 was considered as significant.

Analyzed data was presented in the form of tables, pie charts and graphs.

Linear regression was used and a test of correlation performed by Spearman's coefficient using the SPSS 12 statistics package to describe the relationship between the study equations.

Bias was calculated as the mean prediction error. The precision of equations was assessed on the basis of the degree of spread from expected variation in the estimates and was measured with the R^2 statistic, which indicates the overall fit for the model .The accuracy of each equation, or how well it represents the true renal function was performed using a formulae as described in the definition of terms above.

7.12   Ethical Considerations

The study was carried out after appropriate approval from the Department of Medicine University of Nairobi and KNH Ethical committee. Only patients who gave consent were enrolled in the study.

Study results were disseminated to the health care providers for use in clinical decision- making.

8.0 RESULTS

Within the five months study period (May to September 2008) a total of 267 patients with chronic kidney disease were screened. One hundred and twelve (112) subjects were excluded. Ninety- two of these declining participation due to uncertainty of returning a 24 hour urine sample, majority of whom lived far from Nairobi. Most of these patients had relatively equal male to female distribution. They had satisfied the inclusion criteria and so their exclusion is unlikely to have affected the outcome of this study. Twenty more were excluded, ten due to acute on chronic renal failure, nine had heart failure and one was an amputee.

Twenty nine subjects were lost to follow up. Four died before a urine sample had been collected, while the rest (25) never returned back with a urine sample to be recruited.

Eleven patients had inadequate urine collection of which a repeat sample was not done due to patients limiting logistics.

Hence a total of 115 subjects were evaluated.

FIGURE 1: PATIENTS FLOW CHART
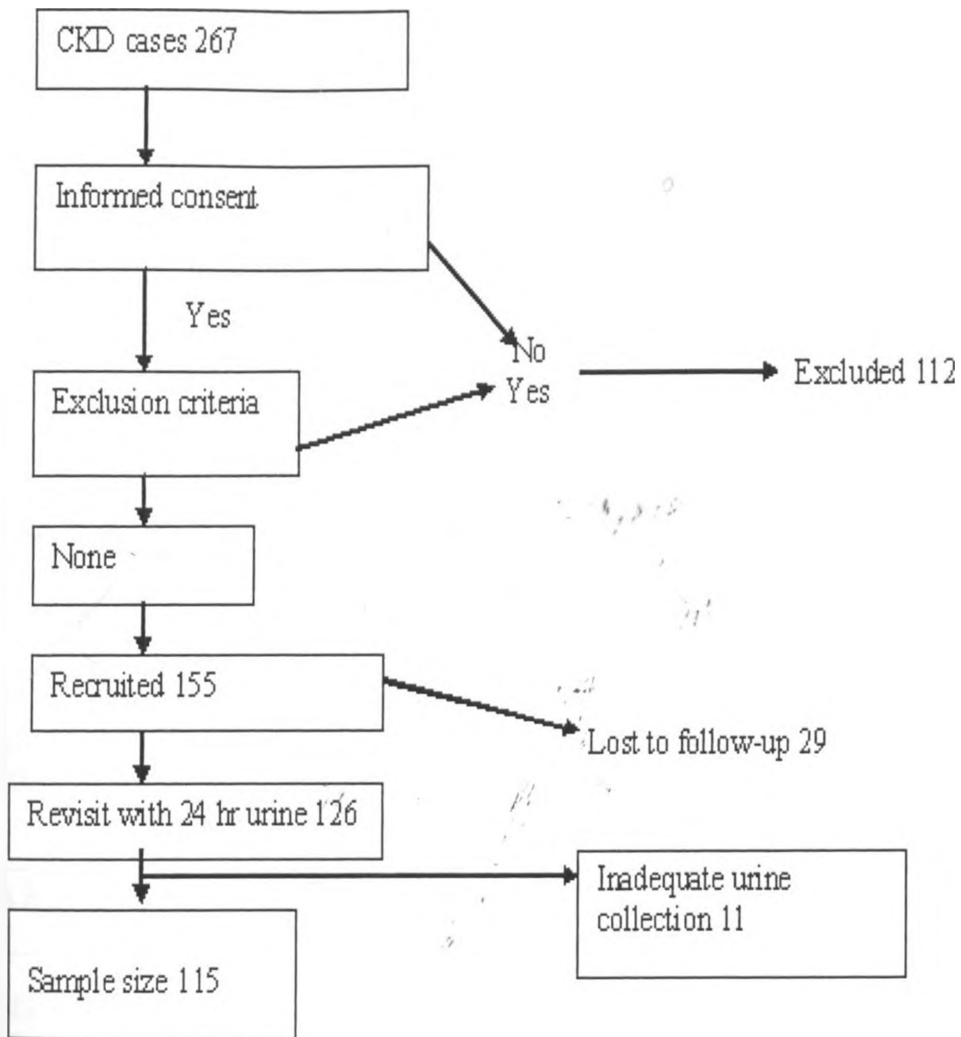
Table 1: BASIC CHARACTERISTICS OF PATIENTS OF PATIENTS WITH CKD

No. of subjects in the study (n)	115
Gender male	64 (55.7%)
Female	51 (44.3%)
Mean age	48.1
Range	18-87
Std deviation	16.612
Hypertensive patients	39 (33.9%)
Diabetic patients	6 (5.2%)
Patients with Hypertension and diabetes	36 (31.3%)
Others(nonhypertensives non-diabetics)	34 (29.6%)

Male to female ratio in this study was 1.25: 1 with a mean age of 48 years and a range

of 18 – 87 years. Subjects with hypertension and diabetes were 31.3% and those without

Diabetes or hypertension 29.6 %.The latter included patients with chronic glomerulonephritis and

others whose eitiology was not identified.

Table 2: SELECTED LABORATORY CHARACTERISTICS OF PATIENTS WITH CKD

VARIABLE	MEAN	MEDIAN	STANDARD DEVIATION	RANGE
SERUM CREATININE(umol/L)	483.5	321.0	444.2	200 - 3132
SERUM UREA(BUN) (mmol/L)	24.4	16.4	21.8	5 - 45
SERUM ALBUMIN(g/L)	36.1	36.6	10.8	2 - 61

The mean serum creatinine concentration was 483.5 umol/L with a range of 200 – 3132 umol/L.
The mean serum urea level was 24.4 mmol/L with values ranging from 5-45 where as the mean
serum albumin level was 36.1g/L with a range of 2-61g/L.

Figure 2: AGE DISTRIBUTION OF PATIENT WITH CKD (N=115)

Age distribution of patients with CKD
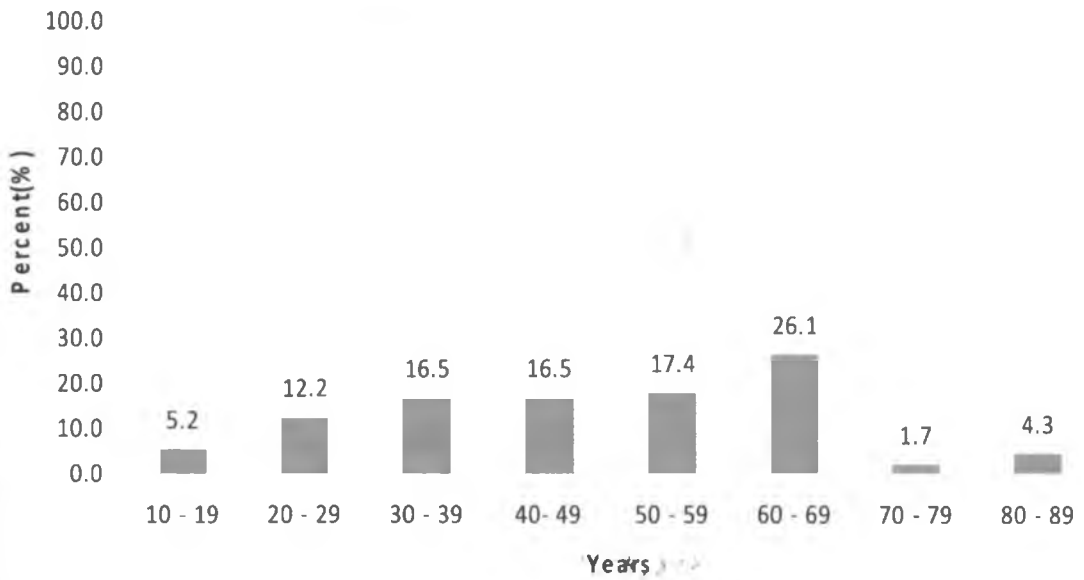
The age-group between 60 -69 years had the highest number of patients represented in this study with 30 subjects constituting 26.1 % of the total. The age-group between 70-79years constituted 1.7% of the study population which was the least represented group category.

TABLE 3: 24 HOURS CREATININE CLEARANCE IN PATIENTS WITH CKD

	N = 115	male	female
Mean Crcl	18.1	19.8	16.0
median	18.2	19.1	17.0
Standard deviation	11.3	12.6	9.1
Range	2.2 – 53.0	2.2 – 53.0	3.0 – 36.9

The mean 24 hour creatinine clearance was 18.13ml/min with a median clearance of 18.10 ml/min. Male and female subjects had a mean creatinine clearance of 19.782 ml/min and 16.015ml/min respectively. The difference in their mean creatinine clearances was not statistically significant (p value 0.077).

Table 4: GFR ESTIMATION USING THE COCKCROFT-GAULT EQUATION AND THE MDRD ORIGINAL AND MDRD ABBREVIATED EQUATIONS (N=115)

GFR estimation equation(ml/min)	mean	median	standard deviation	range
GFR by MDRD(original eqn) (ml/min/1.73m^2)	16.5	17.1	8.8	2.5-45.7
GFR by MDRD abbreviated eqn (ml/min/1.73m^2)	18.4	18.3	9.8	2.0-43.6
GFR by Cockcroft-Gault eqn (ml/min/1.73m^2)	20.1	19.8	10.3	3.4-51.9

The mean estimated GFR were 16.5 ml/min, 18.4 ml/mi, and 20.1 ml/min by MDRD(original equation), abbreviated MDRD and Cockcroft-Gault equations. There was statistical significance in differences of the means estimated between MDRDoriginal and MDRD abbreviated equations, and between MDRDoriginal and Cockcroft-Gault equations, P-values 0.036 and P < 0.001 respectively .The difference between the mean GRF estimated by MDRD abbreviated equation and Cockcroft-Gault equation was not significant,P = 0.087.

RELATIONSHIP BETWEEN 24HR CREATININE CLEARANCE AND COCKCROFT-GAULT EQUATION

FIGURE 3: LINEAR REGRESSION OF 24HOUR CREATININE CLEARANCE AND COCKCROFT-GAULT EQUATION
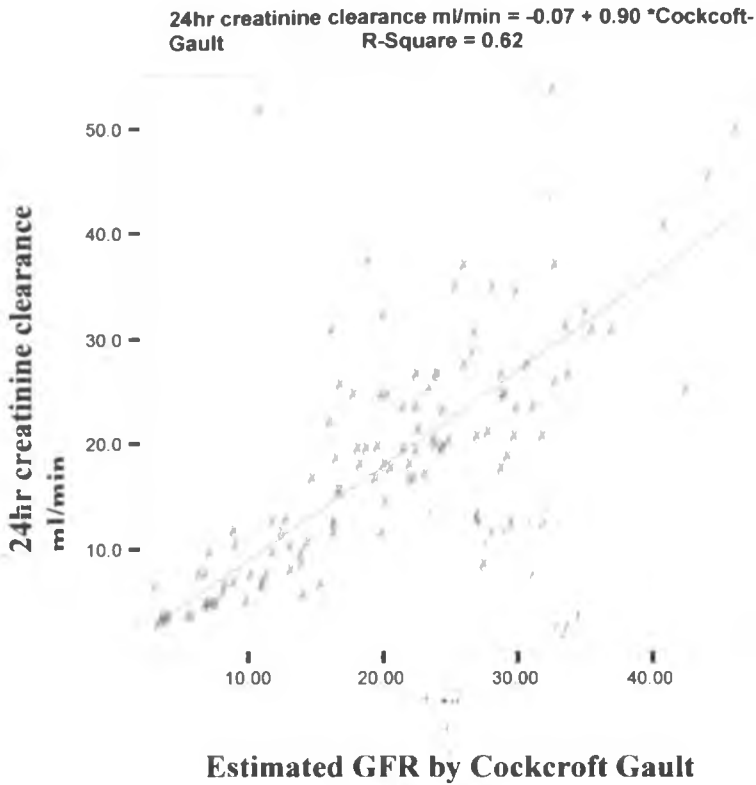
24hr creatinine clearance ml/min = -0.07 + 0.90 *Cockcoft-Gault   R-Square = 0.62

Estimated GFR by Cockcroft Gault

Linear regression performed to establish the relationship between GFR by Cockcroft-Gault and 24hr creatinine clearance.24hr crcl = -0.07 + 0.90(Cockcroft-Gault); R-square = 0.62 is the precision, r = 0.78

p-value = 0.000

RELATIONSHIP BETWEEN 24HR CREATININE CLEARANCE AND MDRD (original) EQUATION

FIGURE 4: LINEAR REGRESSION OF 24HOUR CREATININE CLEARANCE AND MDRD ORIGINAL EQUATION

24hr creatinine clearance ml/min = 0.96 + 1.05 * GFRbyMDRDeqn

R-Square = 0.66

Estimated GFR by MDRD (original equation)
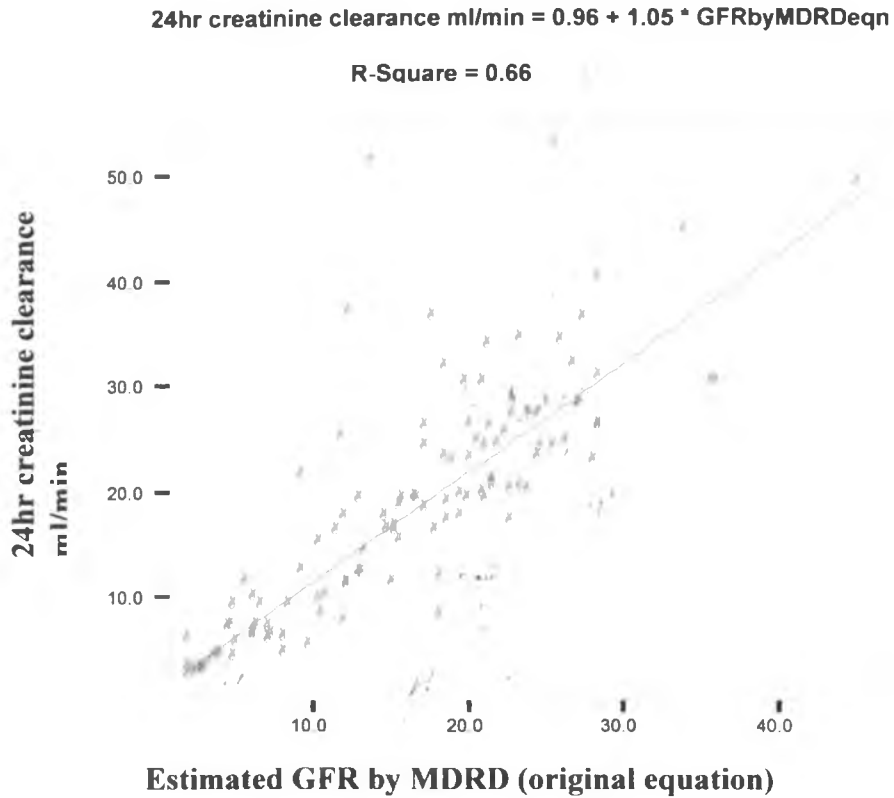
Linear regression performed to establish the relationship between GFR by Cockcroft-gault and 24hr creatinine clearance.24hr crcl = 0.96 + 1.05(MDRD original); R-square = 0.66 is the precision. r =0.81,   P –value= 0.000

RELATIONSHIP BETWEEN 24HR CREATININE CLEARANCE AND MDRD4
(abbreviated) EQUATION

FIGURE 5: LINEAR REGRESSION OF 24HOUR CREATININE CLEARANCE AND MDRD ABBREVITED EQUATION

24hr creatinine clearance ml/min = 1.46 + 0.91 * MRDeqn4

R-Square = 0.63
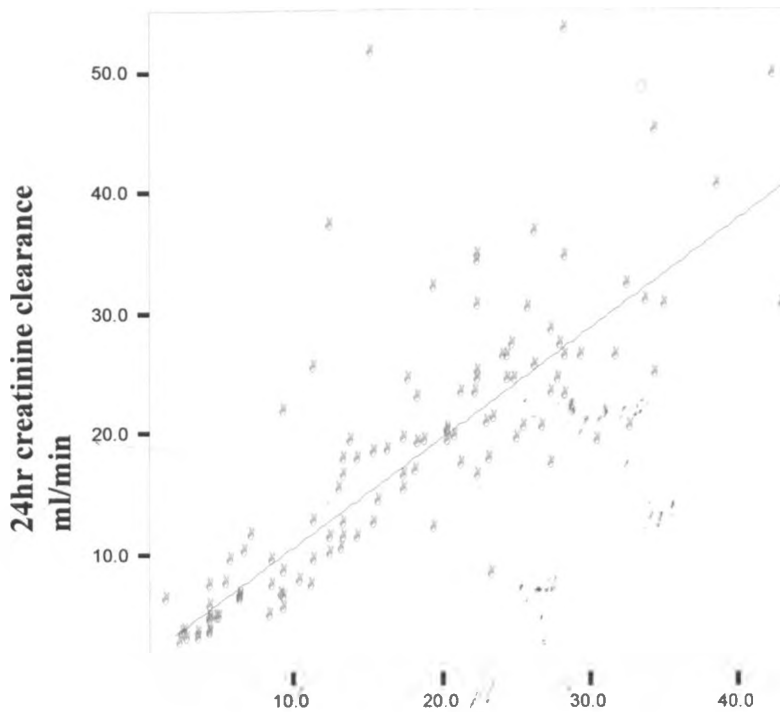
Estimated GFR by MDRD4(abreviated equation)

Linear regression performed to establish the relationship between GFR by MDRD4 creatinine clearance. 24hr crcl = 1.46 +0.91(MDRD4); R-square = 0.63 is the precision. r = 0.79 Pvalue< 0.001

All the three GFR estimating equations demonstrated good precision as described by their R^2 values i.e MDRD original (R^2 =0.66) , MDRD abbreviated (R^2 =0.63) and Cockcroft-Gault (R^2 =0.62)

FIGURE 6: RELATIONSHIP BETWEEN COCKCROFT-GAULT AND MDRD original EQUATION

GFR Cockcroft Gaut (Corrected) = 3.08 + 1.05 * GFRbyMDRDeqn
R-Square = 0.87

Estimated GFR by MDRD (original equation)
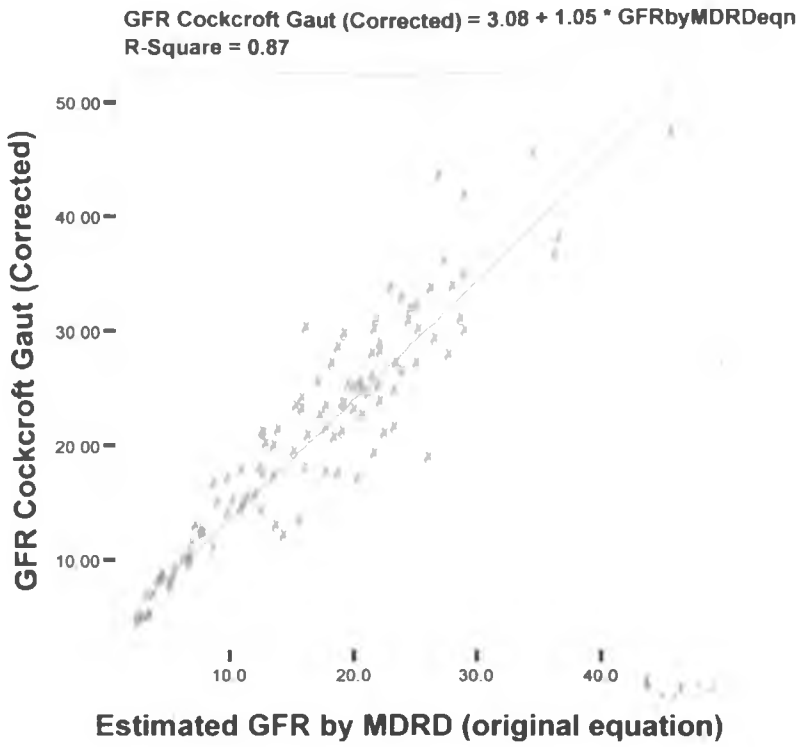
A linear regression between CG and MDRDoriginal equations demonstrated good correlation, R-square = 0.87

FIGURE 7: RELATIONSHIP BETWEEN COCKCROFT-GAULT AND MDRD ABBREVIATED EQUATION

GFR Cockcroft Gaut (Corrected) = 2.96 + 0.94 * MRDeqn4
R-Square = 0.89

Estimated GFR by MDRD4(abreviated equation)
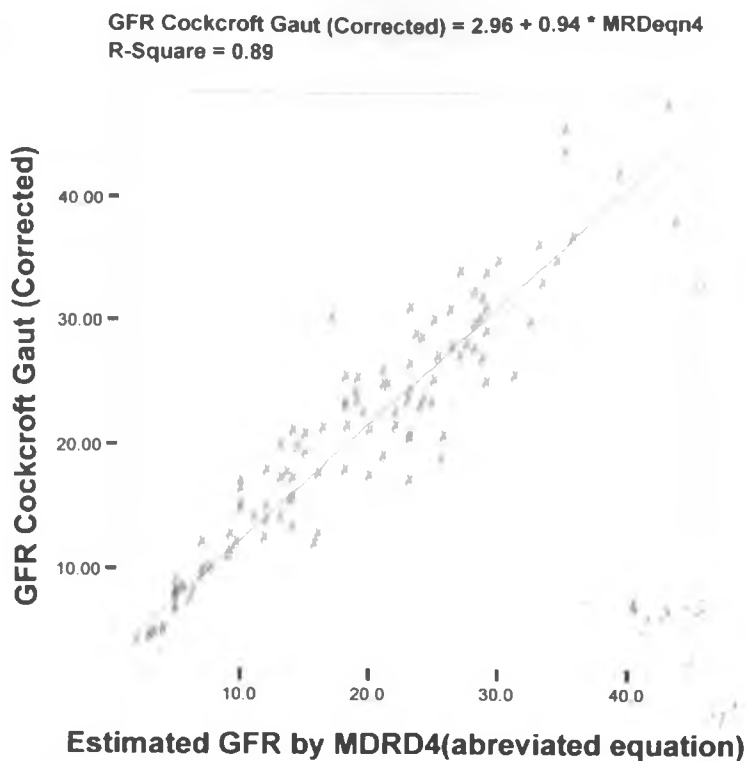
A linear regression between Cockcroft-Gault and MDRD abbreviated equations demonstrated good correlation, R-square = 0.89

FIGURE 8: RELATIONSHIP BETWEEN MDRD ORIGINAL AND MDRD ABBREVIATED EQUATIONS

Estimated GFR by MDRD (original equation) = 0.68 + 0.86 * MRDeqn4
R-Square = 0.93
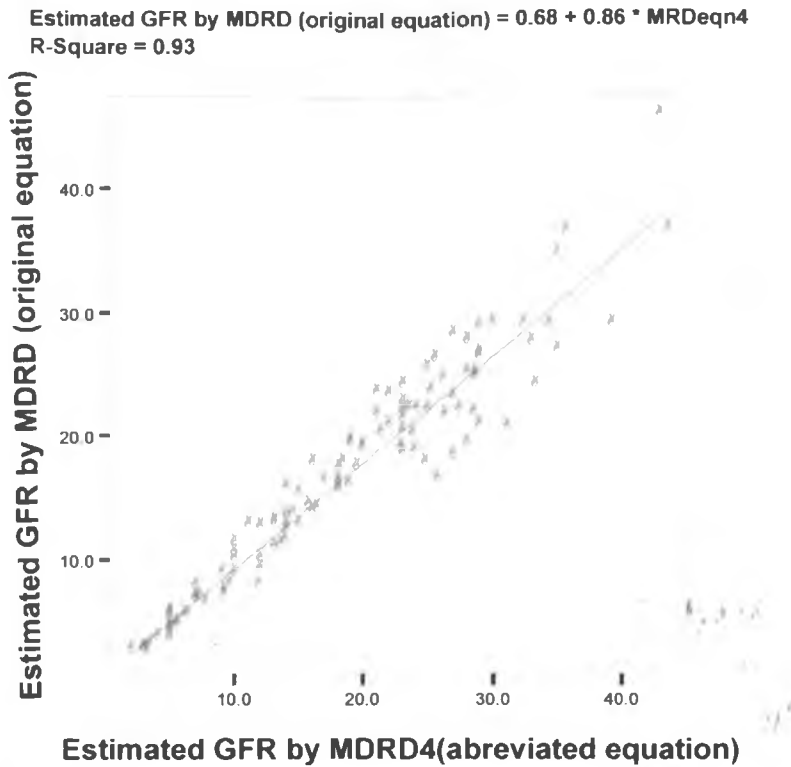
A linear regression between MDRDoriginal and MDRDabbreviated equations demonstrated good correlation, R-square = 0.93

TABLE 5: CLASSIFICATION OF CKD STAGES BY CREATININE CLEARANCE METHOD AND GFR ESTIMATING EQUATIONS

Classification of CKD stages by Creatinine clearance and GFR estimating equations

GFR estimation method (N=115)	Stages of chronic kidney disease		
	Stage 3	Stage 4	Stage 5
24hrs Creatinine clearance	18(15.7%)	52(45.2%)	45(39.1%)
MDRD(original eqn)	4(3.5%)	62(53.9%)	49(42.6%)
MDRD4 (abbreviated eqn)	12(10.4%)	57(49.6%)	46(40%)
Cockcroft-gault eqn	20(17.4%)	54(47.0%)	41(35.7%)

All subjects were classified into stage 3,4 and 5 by the 24 hour creatinine clearance method (measured) and the estimation equations MDRD original and abbreviated and Cockcroft-Gault equations. Majority of the subjects were classified into stage 4 by all methods i.e 45.2% , 53.9% ,49.6% and 47.0% by 24hour creatinine clearance ,MDRD original ,MDRD abbreviated and cockcroft-gault equations respectively.

TABLE 6: ACCURACY OF MDRD ORIGINAL EQUATION

GFR values in % falling within measured 24hr Crcl	Frequency (n=115)	Cumulative Percent
within 30%	90	78.3
within 50%	17	93.0
> 50	8	100

Approximately 78.3% of the GFR results by MDRD original equation were within 30% and 93% being within 50% of the true GFR (as measured with creatinine clearance method) .

TABLE 7: ACCURACY OF COCKCROFT-GAULT EQUATION

GFR values in % falling within measured 24hr Crcl	Frequency (n=115)	Cumulative Percent
within 30%	57	49.6
within 50%	25	71.3
> 50	33	100

Approximately 49.6% of the GFR results by Cockcroft-Gault equation were within 30% and 71.3% being within 50% of the true GFR (as measured with creatinine clearance method) .

TABLE 8: ACCURACY OF MDRD4 EQUATION

GFR values in % falling within measured 24hr Crcl	Frequency (n=115)	Cumulative Percent
within 30%	76	66.1
within 50%	21	84.3
> 50	18	100

Approximately 66.1% of the GFR results by MDRD4 equation were within 30% and 84.3% being within 50% of the true GFR (as measured with creatinine clearance method) .

The MDRD original equation demonstrated the greatest accuracy compared to MDRD abbreviated and Cockcroft-Gault GFR estimating equations.

TABLE 9: BIAS OF EQUATIONS

Bias of MDRD original equation	- 1.7203
Bias of Cockcroft-Gault equation	1.8905
Bias of MDRD abbreviated equation	0.2231

GFR estimated by MDRD abbreviated equation yielded the least biased estimate compared to Cockcroft-Gault and MDRD original equation hence least likely to underestimate or overestimate the measured 24 hour creatinine clearance .

9. DISCUSSION

GFR is traditionally considered the best overall index of kidney function in health and disease. Repeated evaluation of renal function is a very important aspect in the management of many metabolic disorders especially in patients with diabetic related or non-diabetic kidney disease to pre-empt possible renal complications.[57]

There are more than twenty-five GFR estimating formulae described in literature. It is the Cockcroft-Gault and MDRD formulas that have enjoyed worldwide endorsement. Ideal GFR estimation is measured using exogenous filtration markers such as inulin, iohexol, iothalamate, DTPA and EDTA. However, use of these methods is not practical in routine practice due to financial costs and time implications even in rich economies. Little work has been done on establishing the performance of these formulae among black African patients. [59,60,62] This study looked at the performances of the Cockcroft - Gault ,MDRD abbreviated and MDRD original formulae compared to 24 hour creatinine clearance method. All the 3 GFR estimating formulae had strong correlations demonstrating good agreement with the 24 hour creatinine clearance. It was the MDRD abbreviated formula that described the best overall agreement when precision, bias, accuracy and correlation indices were assessed together. These findings have also been observed in several studies. [57,58,61,62]

In our study, these formulae were evaluated in a cohort of 115 subjects with a fairly equal gender distribution, male to female ratio of 1.25 : 1. An important characteristic of this cohort is that it included subjects whose measured GFR ranged from 2.2 to 53 ml/min per 1.73 m^2, which constituted patients in CKD stage 3,4 and 5. Thus, the performances of the Cockcroft-Gault and MDRD formulas could be assessed in subjects with moderate to severe kidney dysfunction. Furthermore, because the patients included in this study were black Africans, the performances of the MDRD and Cockcroft-Gault formulas could be assessed in a group of subjects whose anthropometric characteristics are different from those of other populations. For example, when compared with Jafer et al[57], the mean weight of our study population was lower by 2.34kg (64.36 +/- 10.1 versus 67.5 ± 15.6 kg), whereas, on average, our patients were 7.5 years younger than those included in their study (48.1 ± 16.6 versus 55.6 ± 14.2 yr) and a similar percentage of subjects were male in both cohorts (55.7 versus 54.5%).However they analyzed a wider range of renal function ie creatinine clearance ranging from 2 to 187ml/min per 1.73m2 compared with ours Crcl range of 2.2 to 53ml/min per 1.73m^2.

We studied patients with CKD and upon computation of their variables e.g sex, race, age and various laboratory parameters using the 3 GFR estimating equation they were classified into stage 3, 4 and 5 (table 5).Noting that each GFR estimating formula has intrinsic differences (page 17) the values of GFR as calculated varied when each formula was compared. Majority of the subjects were classified into stage 4 by all 3 methods i.e 45.2%, 53.9% and 47.0% by 24 hour creatinine clearance method, MDRD original, MDRD abbreviated and Cockcroft-Gault equations respectively (table 5).

The mean 24 hour creatinine clearance was 18.13ml/min while the estimated GFR by Cockcroft-Gault and MDRD original and abbreviated equations were 20.073ml/min, 16.46 ml/min and 18.405 ml/min respectively (table 3). These results can be compared with a similar study by Adnan *et al* where mean creatinine clearance was 21.1ml/min by 24 hour creatinine clearance and GFR of 29.1 ml/min,25.9ml/min by Cockcroft-Gault and MDRD abbreviated equations respectively.[61]However, one has to note that Adnan and his group studied patients with a lower cut-off values of serum creatinine compared to our study population i.e serum creatinine > 1.50mg/dl(132.6 umol/L) compared to serum creatinine of >2.26mg/ml(200umol/L) and serum creatinine range of 200 – 3132umol/L in our study (table2). Comparision of the estimation equations revealed strong correlation with creatinine clearance method. MDRD original equation had the best correlation(r = 0.81), followed by MDRD abbreviated(r = 0.79) and Cockcroft-Gault equations(r =0.78){figure 3,4and 5}. Adnan *et al* described correlations of r=0.625 and r= 0.724 for Cockcroft-Gault and MDRD abbreviated equations respectively. [61]

Le Rich *et al* demonstrated that Cockcroft-Gault correlated better with 24 hr creatinine clearance than MDRD abbreviated equation. This is in contrast to our study where MDRD abbreviated equation described better agreement with 24 hour creatinine clearance compared to Cockcroft-Gault equation.This disparity could be explained by several reasons. First, our study looked at patients with moderate to advanced renal dysfunction i.e CKD stages 3 – 5, where as Le Riche and his group studied subjects with CKD stage 1 to 5.Furthermore, they had a high prevalence of patients with normal GFR. It is important to note that the MDRD equations tend to perform poorly in early renal dysfunction hence less reliable in patients with normal renal function or mild renal failure [11,17, 24].Secondly, we excluded patients with underweight where as Le Riche et al also studied subjects with underweight and others with obesity.[62] Weight is an important variable factored into Cockcroft-Gault equation. Therefore patients with extremities of body

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weight will register marked differences in GFR calculated when compared to MDRD formulars which do not compute for weight.

Almond *et al* in a prospective study of 97 patients with CKD and serum creatinine of > 200umol/L demonstrated that the best prediction equation was the MDRD4 which was better than Cockcroft-Gault with and without correction for ideal body weight. Seventy five patients had a combined urea and creatinine clearance of 15ml/min. The MDRD4 equation had a higher NPV (64%) but lower PPV (89%) compared to Cockcroft-Gault equation for identifying patients whose creatinine clearance as < 15min/min.They concluded collection of 24hour urine samples may still have a role in the assessment of the patients with stages 4 and 5 CKD. [63] This study was similar to ours in that patients with serum creatinine of > 200umol/L were analysed where the majority of patients were classified into stages 4 and 5 CKD by the 24 hour creatinine clearance(45.2% and 39.1% respectively).Our study also confirmed MDRD4 equation to be superior to Cockcroft-Gault equation in estimating creatinine clearance in patients with CKD stage 3,4 and 5. These observations further affirms the consistency of MDRD abbreviated equation being superior to Cockcroft-Gault equation in estimating GFR in advanced stages of CKD. [57,58,61,62]

In another work by Ibrahim *et al* the MDRD equation substantially underestimated the measured GFR, where as the Cockcroft-Gault formular underestimated it when it was < 120ml/min per 1.73m2 and overestimated it when measured GFR was > 130ml/min per 1.73 m2. [49]But this was a validation study that computed patients studied in Diabetes control and complication Trial(DCCT) whose serum creatinine was between 1.2mg/dl(106.1umol/L) and 7mg/dl(618umol/L)Furthermore they used iothalamate, an external filtration marker and not serum creatinine, an endogenous filtration marker used in our study.

Ajayi *et al* studied the predictive performance of Cockcroft-Gault fomula in Nigerian patients and described a high correlation between the measured and predicted r =0.86 This study recruited subjects with a wide range of variarion in renal function including patients with congestive heart failure. Neither serum creatinine nor disease state nor level of creatinine had an important effect on predictive value of Cockcroft-Gault equations, the only prediction equation that was studied and compared to 24hour creatinine clearance. In our study patients with congestive heartfailure were excluded and the Cockcroft-Gault equation was corrected for BSA.

These together with the small number patients in their study might explain the slight difference in the coefficients compared to our study. [60]

Mcligeyo studied 76 subjects; 35 healthy and 41 subjects with varying degrees of chronic kidney disease and described correlation between measured (24 hour creatinine clearance) and creatinine predicting equations i.e Hull, Gates and Jellife equations. He reported good correlation between measured GFR and Cockcroft-Gault equation with a correlation coefficient of 0.995 when all subjects were considered and compared to 0.710 when only healthy subjects were considered. [59] He did not analyze the correlation of the unhealthy population. We only studied patients with reduced creatinine clearance(all were unhealthy subjects) and Cockcroft-Gault ,MDRD original and MDRD abbreviated demonstrated good correlations with 24h Crcl. Durakovic reported a correlation coefficient of 0.858 and Hallynic *et al* of 0.91.[66,67] Our study demonstrated a correlation coefficient of 0.781 between 24hour creatinine clearance and Cockcroft-Gault equation.The difference in race and smaller number of subjects studied compared to ours might in part account for these differences.

Aizawa *et al* studied 100 Japanese adults in hospital where both Cockcroft-Gault and MDRD abbreviated equation showed strong correlation (r=0.942 and r= 0.921 by Cockcroft-Gault and MDRD equations respectively. They concluded that predictive formulae could be useful for the prediction of Creatinine clearance in Japanese patients.Despite our study population having more males than females(table 1) similar to Japanese subjects,their study population is notable for men constituting 67% of the study subjects.[58] The normal biophysical characteristics of gender is such that male sex generally has more mass than females. This might in part explain why Cockcroft –Gault formular demonstrated a stronger correlation than MDRD abbreviated equation. Furthermore, most of their patients had lesser degrees of renal dysfunction compared to our study.

The performance of corrected Cockcroft-Gault, MDRD original and MDRD abbreviated equations were assessed by determining the degree of bias, precision and accuracy which varied depending on the type of GFR estimating equation studied.

Bias as indicated by the mean prediction error,was greatest for the Cockcroft-Gault followed by MDRD original and MDRD abbreviated i.e 2.11, -1.720 and 0.223 respectively (table 9).MDRD abbreviated had the least bias. This means that it had the minimum systemic deviation from the

measured creatinine clearance compared to Cockcroft-Gault and MDRD original equation hence least likely to yield a biased estimate of GFR.

The precision is the value of R^2 statistic derived from the linear regression line describing the relationship between measured creatinine clearance and GFR estimating equations (figure 3,4 and 5)). MDRD original had the best precision followed by MDRD abbreviated and Coockroft-Gault equation. Precision expresses the variability (or dispersion) of a prediction equation. Despite being highest for MDRD original formula one cannot on its own make conclusions without interpreting it with the bias and accuracy of the equation.

The relative accuracy was described by the percentage of GFR estimates falling within 30% & 50% of the measured 24h Creatinine clearance. Approximately 78% of the GFR estimates by MDRD original equation were within 30% and 93% within 50% of the measured 24hour creatinine clearance. About 49.6% of the GFR estimate by Cockcroft-Gault equation were within 30% and 71.3% within 50% of the measured 24 hour Creatinine clearance. Sixty-six percent (66.1%) of GFR estimates by MDRDabbreviated equation were within 30% and 84.3% falling within 50% of the measured 24 hour creatinine clearance. This shows that MDRD equations had the greatest accuracy compared to Cockcroft – Gault equation.

These results can be compared to work done by Shoker *et al*.They demonstrated limited accuracy of the Cockcroft-Gault equation to predict creatinine clearance particularly in patients with Crcl below 50ml/min. Less than 1/3 of the calculated GFR values fell within 30% of the measured Crcl. However correction for body surface area demonstrated more accuracy to estimate 24 hour creatinine clearance. They recommended physicians to use the Cockcrot-Gault formular in their practice until more credible formulars are developed. [65]

Jafer *et al* studied migrant population of South Asian origin. The agreement among Cockcroft-Gault and MDRD4 were assessed and the accuracy of estimated verses measured GFR determined.The proportion of estimates within 20,30 and 50% of measured values was 47.7% verses 32.8%, 64.9 versus 49.6% and 79.4% verses 72.9% for Cockcroft-Gault verses MDRD 4 equations respectively .[57] In our study GFR estimates falling within 30 and 50% were 49.6% Vs 66.1% and 71.3 Vs 84.3% for Cockcroft-Gault Vs MDRD4 respectively. This demonstrates that the MDRD abbreviated equation was more accurate than Cockcroft-Gault equation.

Garcia-Naveiro *et al* and group compared 615 estimates of GFR performed by MDRD4 and 24h Crcl method in adults > 18 years with advanced (aCRF)(15-30ml/min/1.73m2)CRF and preterminal (tCRF)(<15ml/min/1.73m2) CRF.In aCRF mean GFR were 19.7ml/min/1.73m2 +/- 5.5 (MDRD4) and 19.3+/- 3.7ml/min/1.73(Crcl). They concluded MDRD4 and 24h Crcl show an acceptable agreement in advanced stages of chronic renal failure. MDRD4 produces estimates of GFR systematically higher than those given by Crcl method in patients with terminal CRF. [64]

Under collection of urine sample could have been a potential source of bias in our study. This was however limited by emphasis to patients and/or their caretakers on adequacy of urine collection and advised appropriate recollection in the cases of doubt.

Study by Jafer *et al* deleted samples that contained values of 24h urine creatinine excretion at the 10th percentile or less of the distribution of urine creatinine levels.[57] This could have been a better indicator of adequacy of urine collection compared to relying on 24 hour volume of urine collected had we applied it in our study, however, no validated Normogram reference values of 24 hour urine creatinine excretion for black Africans are available.

Other explanation of differences in estimating GFR could be explained in some high risk subset, including elderly patients and those presenting markers of a poor nutritional condition. Garcia et al concluded in their study that GFR should be estimated using Crcl rather than MDRD equation in patients with terminal CRF or GFR < 15 ml/min as also in older and malnourished patients with advanced CRF (GFR 15- 30ml/min) as this may represent a more conservative and safer approach at the time of planning initiation of renal replacement therapy. [64]

10.0 CONCLUSION

1. The GFR estimating equation MDRD original equation, MDRD4 and Cockcroft-Gault formulae had good agreement in estimating GFR at CKD stages 3,4 and 5.

2. MDRD original equation demonstrated the best accuracy and precision followed by MDRD abbreviated and Cockcroft-Gault equations.MDRD abbreviated formular had the least bias and has the added advantage of requiring less variables making it the best tool compared to the rest in predicting creatinine clearance in patients with   CKD stage 3,4 and 5.

10.1   RECOMMENDATIONS

1. The MDRD original, MDRD abbreviated and Cockcroft-Gault equations can be applied to predict 24hr creatinine clearance in Africans with stage 3, 4 and 5 CKD.

2. Although MDRD equations demonstrated better accuracy, utility of corrected Cockcroft-Gault is practical in less privileged economic settings. MDRD abbreviated equation can also be applied by having an MRDR calculator that is readily downloadable from the internet without any charges.

3. A larger study designed to look at subjects with different renal functions e.g CKD stages 1,2 and healthy population will be useful to determine how these equations perform at those levels of kidney function.

10.2   STUDY LIMITATIONS

The standard for diagnosis of reduced GFR in this study was based on measured creatinine clearance(using creatinine as the endogenous filtration marker) but not the gold standard for measuring GFR(using exogenous filtration markers). Creatinine clearance tends to overestimate GFR especially in patients with reduced GFR ,therefore the true value of reduced GFR is likely to be greater.

We cannot exclude the possibility of under collection of urine samples.

11.   APPENDIX 1

STUDY   PROFORMA

Name of patient (participant)……………………………….……..IP

no………………participants Tel.no……………

KNH Ethical Research committee contact 2726300.ext 44355; investigators contact 0725273902

Demographic data

1.Age(yrs) ……

2.Sex (M=1,F=2)

3.Marital status

(single=1,married=2,divorced=3widowed or widower=4)

4.Place of residence……

HISTORY

Hypertension

5.Are you hypertensive? Yes……No …….

6.How long have been diagnosed with hypertension?(yrs)….

Diabetes

7.Are you a diabetic? Yes…..No…..

8.How long have been diagnosed with diabetes?(yrs)…..

Family and social history

9.Are there any 1st degree relatives with hypertension?Yes….No…..

10.Are there any 1st degree relatives with diabetes? Yes…..No…..

11.Are you aware that chronic kidney disease has different stages of disease progression? yes....No….

12.When were you referred to the renal clinic or K.N.H due to kidney disease.

13.Are you aware of what is renal replacement therapy? Yes….No….

Examination

14.weight (kg) ….

15.height (cm)….

16.BP (mmHg):1st reading …. 2nd reading….   Average…..

Laboratory Results

17.serum creatinine (umol/L)….mg/dl….

18.serum BUN (umol/L)….mg/dl….

19.serum albumin (g/dl)….

20.24hr creatinine clearance (ml/min)….

21.estimated GFR by MDRD equation (ml/min)….original eqn…. MDRD eqn 4……

22.estimated GFR by cockcroft-gault equation(ml/min)….

12.   APPENDIX 2

CONSENT EXPLANATION FORM

My name is Dr. Emmanuel Ndosi. I am a Post Graduate doctor studying at the University of Nairobi. I would like to introduce you to a study I am conducting, entitled

PERFORMANCE OF COCKCROFT-GAULT AND MODIFICATION OF DIET IN RENAL DISEASE EQUATIONS VS 24HOURS CREATININE CLEARANCE IN AFRICANS WITH CHRONIC KIDNEY DISEASE AT KENYATTA NATIONAL HOSPITAL.

What is the study about?

The study is about testing the validity or performance of two formulae(that have been adopted from a different population) in native african patients with chronic kidney disease.

What does the study involve?

The study involves taking history from you,examining you which will include taking your weight,height and blood pressure.It also involves taking about 2mls of your blood sample for measurement of creatinine,albumin and urea.You will also be given a container and instructed on how you will do a 24 hr urine collection which be submitted back to me or my assistant.This urine sample will be studied to obtain a 24hr creatinine clearance.

All information you shall provide shall be kept confidential.

Are there any dangers involved?

Apart from the slight pain of taking your blood, there are no dangers involved.

Will I benefit from the study?

Yes. After analyzing this study results we will be able to generate new suggestions on whether there is a need to have a new or modified formula that conforms with our population which will have important implications on cost of therapy and other interventions including early detection of chronic kidney disease.

Can I withdraw from the study?

You are free to withdraw from the study and this shall not affect your care or treatment.However we encourage you to remain in the study for your benefit and the benefit of other patients.

Thank you for your co-operation.

13.   APPENDIX 3

CONSENT FORM

Name:…………………………….. **Age:**…………………………………

Number:…………………………..

I, the above named, have been requested to take part in a study concerning comparison between two equations in African populations with chronic kidney disease. These equations are routinely used to measure the severity of kidney disease. This will involve taking a full history, general examination including blood pressure, weight, height. This study will also involve taking a sample of my blood (2mls) for assessment of creatinine, albumin and urea. I will also be required to submit a 24 hr collection of urine. The results shall be confidential.

This will put me at no risk.

I understand that I am free to either agree or refuse to participate in the study and this shall not interfere with my medical care.

Having agreed on the above I voluntarily agree to participate in the study.

Sign………………………….. Date…………………………..

14.0   Research Participant statement:

I ……………………................have fully understood the purpose and implications of this study and I am willing and ready to participate.

Sign…………

14.1 Investigator's statement:

I the investigator have educated the research participant on the purpose and implications of this study.

Sign…………

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21st May, 2008

Dr. Emmanuel Kisali Ndosi
Dept. of Medicine
College of Health Sciences
UNIVERSITY OF NAIROBI

Dear Dr. Emmanuel

RESEARCH PROPOSAL: "PERFORMANCE OF THE COCKCROFT-GAULT AND MODIFICATION OF DIET IN RENAL DISEASE EQUATIONS IN NATIVE AFRICANS WITH CHRONIC KIDNEY DISEASE AT KENYATTA NATIONAL HOSPITAL" (P6/1/2008)

This is to inform you that the Kenyatta National Hospital Ethics and Research Committee has reviewed and **approved** your above revised research proposal for the period 21st May, 2008 – 20th May, 2009.

You will be required to request for a renewal of the approval if you intend to continue with the study beyond the deadline given. Clearance for export of biological specimen must also be obtained from KNH-ERC for each batch.

On behalf of the Committee, I wish you fruitful research and look forward to receiving a summary of the research findings upon completion of the study.

This information will form part of database that will be consulted in future when processing related research study so as to minimize chances of study duplication.

Yours sincerely

PROF A N GUANTAI
SECRETARY, KNH-ERC

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