Concordance between Modification of Diet in Renal Disease and Cockcroft-Gault formulas in chronic kidney disease patients at St. Paul's Hospital Millennium Medical College

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This is to certify that the thesis prepared by Hunduma Dinsa, entitled: Modification of Diet in Renal Disease versus Cockcroft-Gault formulas in chronic kidney disease patients at St. Paul's Hospital Millennium Medical College and submitted in partial fulfillment of the requirements for the Master of Pharmacy degree in Pharmacy Practice complies with the regulations of the University and meets the accepted standards with respect to originality and quality.

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Abstract

Concordance between Modification of Diet in Renal Disease and Cockcroft-Gault formulas in chronic kidney disease patients at St. Paul's Hospital Millennium Medical College

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Currently the two most commonly used glomerular filtration rate estimating equations for drug dosing are the Modification of Diet in Renal Disease (MDRD) and Cockcroft-Gault(CG) formula. However there is still a concern about whether to use MDRD interchangeably with CG for drug dosage adjustment. The study was initiated to determine the concordance between MDRD and CG formula and associated factors in chronic kidney disease patients at Saint Paul's Hospital Millennium Medical College (SPHMMC), Addis Ababa, Ethiopia. Design was cross sectional study which involved patient chart review and self administered questionnaire for physicians working in the renal clinic during the study period. Among the total of 422 patients, 249 (59%) were males. Mean age of patients was 46.09 years. The use of MDRD formula for drug dose adjustment by physicians working in the renal clinic of SPHMMC was six out of nine physicians. The Pearson correlation coefficient between the CG and the MDRD formula was r=0.94, P<0.0001.The concordance between the CG and MDRD formula for FDA assigned kidney function categories and drug dosing recommendation were 73.7%, Kappa=0.644 and 89.6% , kappa=0.782 respectively. Age >70 years was associated with discordance between CG and MDRD formula for drug dosing recommendation whereas serum creatinine 1.2-3.5 mg/dL, weight <61 Kg and age >70 years were associated with discordance between the two formula for FDA assigned kidney function categories. Therefore MDRD formula can be used interchangeably with CG formula for drug dosing recommendation in all adult patients between the age of 18 and 70 years.

Key words: MDRD, CG, drug dose adjustment, concordance.

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Acronyms

AOR	Adjusted Odds Ratio
BSA	Body surface area
CG	Cockcroft-Gault
CGIBW	Cockcroft-Gault adjusted for ideal body weight
CI	Confidence Interval
CKD	Chronic Kidney Disease
COR	Crude Odds Ratio
CrCl	Creatinine Clearance
eGFR	Estimated Glomerular Filtration Rate
FDA	Food and Drug Administration
GFR	Glomerular Filtration Rate
IDMS	Isotope Dilution Mass Spectrometry
KDOQI	Kidney Disease Outcome Quality Initiative
MDRD	Modification of Diet in Renal Disease
NHANES	National Health and Nutrition Examination Survey
NKDEP	National Kidney Disease Education Program
NKF	National Kidney Foundation
SD	Standard Deviation
SPHMMC	St. Paul's Hospital Millennium Medical College

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1. Introduction

1.1. Background

Chronic kidney disease (CKD) is the presence of kidney damage or a reduction in the glomerular filtration rate (GFR) for three months or longer. It is a significant and widespread health problem with growing incidence and prevalence worldwide (Negri *et al.*, 2005). The estimated overall prevalence of CKD (glomerular filtration rate <60 mL/min/1.73 m2) in adults (aged≥18) is increasing exponentially in the older population (Kondo *et al*., 2014). Although kidney is the major organ that plays an important role in the disposition of many drugs (Alahdal and Elberry, 2012), its impairment is an important global health problem which leads to medication dosing errors contributing to the major reasons for hospital admission *(*Leendertse *et al*., 2012).It is estimated that 10% of the population has some kind of renal impairment (Prajapati and Ganguly, 2013). Medication dosing errors are the most important drug-related problems in patients with renal impairment (Getachew *et al*., 2015)

Renal impairment is among important therapeutic problems often under diagnosed despite established classifications, necessitating attempts to improve drug dosing and disease management in kidney dysfunction (Emami *et al.*, 2012). Age-related decline in kidney function is seen in a substantial portion of the older population. Accurate estimation of kidney function is especially important in this population because these older adults consume nearly 34% of all prescription drugs and the elimination of many of these drugs depends on the kidneys (Dowling *et al*., 2013).

Cockcroft-Gault equation remained the most common method for bedside estimation of GFR because it is very easy to use without a calculator or computer. This advantage of Cockcroft-Gault formula is keeping it alive in spite of the rapid popularity of MDRD formula (Ali *et al.*, 2013). On the contrary, the routine reporting of eGFR for adults based on an IDMS-traceable creatinine is

becoming the clinical standard for patient care (Narva, 2009). The availability of new formula, such as the MDRD combined with the inherent inaccuracies of the original CG formula has led to variable practices among clinicians and institutions, despite the lack of data supporting their use in drug dosing (Bookstaver *et al.*, 2008). The Cockcroft-Gault equation is no longer recommended because it was developed before the standardization of creatinine assays and is less accurate; however, the preference for which estimate to use varies widely among institutions, and the Cockcroft-Gault equation is still often used in clinical practice and in pharmacokinetic studies (Jessica *et al.*, 2015). Currently, no prospective pharmacokinetic studies have been conducted with use of the MDRD equation to generate dosing recommendations, and limited data are available to support its use in some patient populations representing demographic extremes. Collectively, these issues have resulted in considerable confusion among clinicians and have fueled a healthy debate on whether or not to use the MDRD equation to determine drug dosages (Heather *et al.*, 2011). As several equations for quick assessment of kidney function by estimating glomerular filtration rate (eGFR) and several different clinical recommendations for drug dose adjustment in renal failure are published, choosing the correct approach for drug dosage is difficult for the practitioner (Linde *et al*., 2013). Hence, many clinicians are reluctant to use them for this purpose because the FDA Guidance for Industry, and consequently dosing adjustments listed in product labels for most medications, recommends using the CG equation(Stevens *et al*., 2009).

1.2 Statement of the problem

Glomerular filtration rate (GFR) is considered as the best overall indicator of kidney function in healthy people and patients. However, GFR can't be measured easily in the clinical setting; instead, it is estimated with GFR estimating equations. Most commonly used GFR estimating equations are Cockcroft-gault (CG), Modification of diet in renal disease (MDRD) and chronic kidney disease epidemiology (CKD-EPI).These GFR estimating equations are affected by physiologic variables (age, race, sex, muscle mass, weight and height) of an individual. They have different qualities and significant limitations in the estimation of GFR. Furthermore, they are not accurate in the population that are different from those in which the equations were developed(Addisu, 2014).The effort to improve the identification and management of patients with CKD is therefore based on implementing more precise means of assessing kidney function and kidney damage in the clinical setting (Narva, 2009). On top of this, patients with CKD require appropriate medication dosing for disease severity and level of renal function for avoiding adverse drug events, preventing additional renal injury, and optimizing patient outcomes (Long *et al.*, 2004).

Hence, currently the two most commonly used GFR estimating equations for drug dosing are the MDRD and CG formula (Ali *et al*., 2013). However, there is continued debate over which formula more accurately estimates renal function (Melloni *et al.*, 2008). International and national organizations recommend that clinical laboratories report estimated GFR when serum creatinine is ordered and surveys from College of American Pathologists suggest that 70% of clinical laboratories in the United States report eGFR using the MDRD Study equation(Stevens *et al*., 2009).As with all changes in clinical practice, the implementation of eGFR reporting and

creatinine standardization has created some uncertainty and confusion among health care providers. A focus of concern is the assessment of kidney function for drug dosing adjustment (Narva *et al.*, 2009).There is understandable concern about whether to change the conventional use of CG in drug dosage adjustment to the use of the readily available MDRD(Gill *et al*., 2007). It is important to know factors affecting the preference of one formula over the other (Williamson *et al*., 2008).

Numerous studies were done to compare these two equations for drug dosing recommendations in various settings. However there is still no study done in Ethiopia, to compare the agreement between the MDRD and CG formula for drug dosing purpose. Since the mean weight of the population in which the MDRD formula was developed is equal to 80 Kg which is high the concordance may be different in Ethiopians. The aim of this study is to evaluate if CG equation might be replaced by the MDRD equation for dosage adjustment in CKD patients treated with nephrotoxic or high renal clearance drugs. The national kidney disease education program (NKDEP) has published an educational advisory on estimating kidney function for drug dosing purpose. The advisory encourages the use of MDRD or CG estimating equation. But there are various controversies on the use of MDRD formula for drug dosing recommendation by the health care provider. Therefore this study potentially reveals to what extent the MDRD formula is concordant with CG formula for drug dosing adjustment in CKD patients.

1.3 Literature review

1.3.1 Prevalence of renal impairment

According to United State Renal Data System (USRDS), prevalence of CKD increased by 20-25% every year in the United States (Iskandar *et al*., 2012).The prevalence of CKD from the National Health and Nutrition Examination Survey (NHANES III) study from 1988 to 1994, a cross-sectional representative survey in USA, was 0.2% in the age group 20–39 years, 1.8% in the age group 40–59 years, 7.6% in the age group 60–69 years, and 24.9% in persons with age 70 and older as determined by means of the MDRD equation (Rothenbacher, 2008). In the United States, the estimated prevalence for CKD in adults is 13% (Erler *et al*., 2012). As estimated in the NHANES study, the prevalence of renal insufficiency with a GFR under 60 mL/min is 11% to 13% and some 20% of all hospitalized patients have impaired renal function (Hartmann *et al*., 2010). To determine the global prevalence of CKD, a systematic review and meta-analysis was conducted by Nathan et al through literature searches in 8 databases comprising 6,908,440 patients. They found that CKD prevalence by stage based on KDOQI criteria shown in table 1 below, was Stage-1: 35%; Stage-2: 39%; Stage-3: 76% ; Stage-4: 4% and Stage-5: 1% (Nathan *et al*., 2016).

In developing nations, the growing prevalence of chronic diseases such as CKD has severe implications on health and economic output. Systematic review and Meta analysis done in sub-Saharan Africa has shown that CKD is a substantial health burden with risk factors that include communicable and non-communicable diseases in which the overall prevalence of CKD from the 21 medium-quality and high-quality studies was 13·9% (Stanifer *et al*., 2014). In their study Decloedt et al, also found renal impairment in 32% of medical admissions (Decloedt, *et al*., 2010).Using MDRD formula, among 422 patients with serum creatinine≥1.2 mg/dL, renal impairment (GFR≤50ml/min) was identified in 54.7% of patients (Gidey *et al*., 2015).Study done

in internal medicine ward using CG equation shows that nine percent of medical admissions were found to have renal impairment (CrCl≤ 59 ml/min) (Getachew *et al*., 2015). Another study was done in Butajira hospital of southern Ethiopia in which from a total of 214 diabetics attending the follow-up clinic CKD was present in 18.2 % and 23.8 % of the study participants according to the MDRD and CG equations, respectively (Fiseha *et al.*, 2014). The rapid rise of common risk factors such as diabetes, hypertension, and obesity, especially among the poor, will result in even greater and more profound burdens that developing nations are not equipped to handle (Nugent *et al.*, 2011). These underlying conditions leads to the complication of drug therapy as variety of nephrotoxic pharmacological drugs are employed in these patient groups.

Table 1: The National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) classification of chronic kidney disease (CKD)(Hartmann,*et al*, 2010)**:**

Stages of Chronic Kidney Disease		
Stage	Description	GFR
1	Kidney damage with normal or increased GFR	≥ 90
2	Kidney damage with a mild decreased in GFR	60-89
3	Moderate decreased in GFR	30-59
4	Severe decreased in GFR	15-29
5	Kidney failure;GFR<15 or need for dialysis	<15

(GFR is expressed in mL/min/1.73m2 of body surface area)

1.3.2 Assessment of kidney function

Patients with CKD may experience accumulation of metabolite(s) as well as the parent compound. This may result in unexpected cost as the metabolites of some drugs have significant pharmacologic activity (Matzke *et al*., 2011). In order to solve this issue CG and MDRD are the two frequently utilized formulae in clinical practice for estimation of renal GFR (Melloni *et al*., 2008).Creatinine clearance (CrCl) measurement using 24 hours urine collection is mainly neglected in favor of the MDRD and CG formulae, largely because of difficulties in accurate collection of 24 hours urine (Ali *et al.,* 2013). In 1999 the MDRD formula was developed and is nowadays recommended for eGFR reporting in adults by the NKDEP and by the Department of Health in the United Kingdom (KDIGO, 2013).There is compelling evidence for the use of the MDRD equation in stages 3, 4 and 5 of CKD where it provides a less biased, more precise and accurate prediction of GFR than estimates using the CG equation (Devaney and Tomson, 2006). The MDRD equation has its origin from a cohort of outpatients based on ^{125}I iothalamate clearances with moderate-to-severe renal impairment. An abbreviated 4-variable MDRD equation uses only age, sex, race, and serum creatinine level to estimate the renal function (Devaney and Tomson, 2006; Sunder *et al*., 2014). The MDRD equation is recommended by the NKF as more accurate for estimating GFR and is currently generated in many laboratory reports (Melloni *et al*., 2008). It was also shown in various studies that the MDRD formula gives a more accurate estimate of GFR in patients with CKD and therefore it is used for estimating CrCl in CKD and patients with no weight record available (Levey *et al*., 1999; Emami *et al*.,2012).

Although the KDOQI clinical practice guideline advocates the use of the traditional CG equation or MDRD study equation for routine estimation of GFR, the MDRD equation has been proven to

be superior to the CG equation in patients with a GFR lower than 60 mL per minute per 1.73 m^2 (Munar and Singh , 2007).It resulted in the most exact diagnosis for values between 15 and 60ml/min/1.73m^2 (Arrabal-durán *et al.*, 2014).When corrected for creatinine calibration and body surface area in CKD patients, the correlation of CG and MDRD is very high (r^2=0.92) (Gill,*et al*., 2007). According to Ali et al, the correlation (r) between eGFR by MDRD and eGFR by CG equation for CKD stages 1 to 5 was 0.64; 0.31; 0.32; 0.67; and 0.45 respectively (Ali *et al.*, 2013). However, Linde et al found that the overall correlation between MDRD and CG formulas was r=0.87 , CI (0.81-0.91) (Karsch-völk *et al*., 2013).

The MDRD Study equation was proved to be useful in adults while the Schwartz is useful in children. The MDRD equation is as follows:

GFR (ml/min per 1.73 m2) = 186 x $Scr^{-1.154}$ x $age^{-0.203}$ multiplies if female by 0.742 and multiplies for black by 1.210

1.3.3 Concordance between MDRD and CG for drug dose adjustment

Patients with renal insufficiency are at risk of inappropriate drug dosing as many drugs and/or their metabolites are eliminated through the kidneys, implying a need for dose adjustment or drug discontinuation (Nielsen *et al*., 2014).The accumulation and toxicity of many drugs can develop rapidly if dosages are not adjusted in patients with renal impairment (Fanak *et al*, 2012). Hence, appropriate drug selection and dosing in CKD patients is important to avoid unwanted effects of drugs and to ensure optimal patient outcomes. Efforts to reduce dosing errors have the ability to lower the rate of adverse drug events, reduce the cost and improve the overall delivery of healthcare (Hassan *et al*., 2009).For renally eliminated medication, dosage adjustments are necessary to prevent the adverse effects associated with overdosing (Leendertse et al.,2012).Dosages of drugs cleared renally are based on renal function calculated as GFR or CrCl.

The various published studies spot light on the discordance between drug doses recommendation derived from the MDRD equation and CG, commonly reporting rates ranging from 10%-40%, and speculate on the potential dangers of such differences (i.e., adverse patient outcomes).According to Narva et al., concordance for drug dosing recommendations based on measured GFR for the 15 renally cleared drugs was also best for MDRD (88%) compared to CGIBW (82%) and CG (85%) (Narva, 2009).Of the three estimating methods, the CG equation was most likely to generate higher recommended drug dosages and CGIBW was most likely to generate lower recommended drug dosages. But overall concordance of recommended drug dosing was 89% between the MDRD and CG equations. The MDRD produced recommendations that were lower than CG in 9% of the study population and higher in 10% when CGIBW was used. A study of 409 elderly patients with CKD demonstrated excellent correlation between the MDRD and CG formulas. In applying these formulas to dosage adjustments of 8 selected antimicrobials in this same population, 25% of drug dosage calculations differed between the 2 formulas (Bookstaver *et al*., 2008).The use of MDRD equation for drug dosing adjustment in renal impairment patients is encouraged. Implementation of the CKD-EPI formula in place of MDRD doesn't have much clinical impact on this specific application since drug dose adjustment is rarely needed for patients with GFR>60 ml/min. The national kidney disease education program (NKDEP) has published an educational advisory on estimating kidney function for drug dosing purpose. The advisory encourages the use of MDRD or CG estimating equation (Turner, 2016).

During dose adjustment either the dose of a drug must be reduced in inverse proportion to the half-life, or else the interval between doses must be prolonged proportionally to the half-life. Of the 502 studied drugs, 39% required dose adjustment where 46.9% were adjusted and 53.1% were not adjusted correctly (Alahdal and Elberry, 2012) . In study done in Paris, France, 34% of

prescription were inappropriate (14% being contraindicated and 20% with inappropriate dosage given the patient's renal function (Salomon *et al*, 2003).

If the GFR is below 60 mL/min, or if the patient is in CKD stage 3 or higher as shown in table 1 above, certain drugs should no longer be given, either because they tend to damage the kidneys or because they are insufficiently eliminated by poorly functioning kidneys and will therefore accumulate in the body and cause toxic side effects on other organs (Hartmann *et al*., 2010).Therefore safety concern is warranted in patients with GFR less than 60mL/min.

1.3.4 Factors associated with concordance between Cockcroft-Gault and Modification of Diet in Renal disease

The use of MDRD or CKD-EPI in place of the CG equation for recommendation of drug doses in patients with renal impairment is widely discouraged, and a report by the FDA cautioned against this practice. Amazingly, in 2010, the NKDEP suggested that the eGFR (MDRD) and CG can be used interchangeably for the purpose of drug dosing recommendation(Dowling *et al*., 2013).

In addition, several studies support, the equation of CG, used in practice to estimate creatinine clearance from the age, weight and serum creatinine, is unreliable in older people. Similarly, study done by Pedone et al reported that in middle age kidney failure patients of 78 years, the degree of discrepancy found between the MDRD and CG is strongly influenced by age. He also observed that, the more the subject has the characteristics of geriatric patient (advanced age, low weight), the more the difference between the results of the MDRD formulas and CG is great, and the estimation of GFR by the MDRD is high compared with that of CG (Pedone et al., 2006). The MDRD formula has been widely studied in obese Caucasians. The majority of studies reported

superiority of the MDRD formula on CG formula in these subjects (Eric *et al.*, 2015). The difference between CG and MDRD is influenced by patient age, weight, and gender. Most prominent differences were noted in aged and under-weighed subjects. According to Mcfarlandet al, the greatest discrepancy between eCLCr and eGFR-BSA was observed in individuals over 75 years of age (Mcfarlan *et al.*, 2012).

2. Objectives

2.1. General objective

- To determine the concordance between Modification of Diet in Renal Disease and Cockcroft-Gault formula and associated factors in chronic kidney disease patients at St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia.

2.2. Specific objectives

- To determine the prevalence of use of Modification of Diet in Renal Disease formula by physicians for drug dosing.
- To determine the correlation between estimated glomerular filtration rate by Cockcroft-Gault and modification of diet in renal disease formulas.
- To determine the concordance between Cockcroft-Gault and modification of diet in renal disease formula.
- To identify factors associated with the concordance of the two formulas.

3. Methodology

3.1. Study area and period

The study was conducted at St. Paul's Hospital Millennium Medical College which is one of the referral hospitals in Addis Ababa under the Ethiopian Federal Ministry of Health (FMOH). It is the second largest public hospital in the nation, built by the Emperor Haile Selassie in 1961 with the help of the German Evangelical Church. The hospital was established to serve the economically under privileged population, providing services free of charge to about 75% of its patients. In 2007 it became a medical college and its core services include the provision of medical care, teaching and research. The hospital has 337 beds with over 1486 clinical and nonclinical staffs and 13 departments including diagnostic laboratory and its new hemodialysis and renal replacement units. Kidney dialysis treatment was started at the Saint Paul Hospital in September 2014 with the help from the Egypt Government and selected doctors at St. Paul's Hospital in Ethiopia conducted the first successful kidney transplant on September 27, 2015 and the transplant was performed for twenty one people so far. According to the nine month report of policy and plan directorate of the hospital compiled on April 2014, the hospital provides service to an estimated 169,204 people annually who are referred from all over the country. On average 280 patients per month visit the renal clinic of SPHMMC. The study was conducted at SPHMMC from July, 2016 to September, 2016.

3.2. Study design

Hospital based prospective cross-sectional survey was conducted through structured check list which involved patient card review.

Weight and height of the individual patient was obtained by calibrated balance that was available in the renal clinic. For each patient in the study, eGFR was calculated using both the Cockcroft-Gault and the MDRD methods; eGFR using MDRD=186× **(creatinine/88.4) −1.154×age−0.203× (0.742 if female) × (1.21 if black).** The result was expressed in mL/min/1.73 m2.eCrCl using Cockcroft-Gault= **[(140−age) × weight in kg]/72× serum creatinine × (0.85 if female).** The result was expressed in mL/min. From among sampled patient cards which fulfill the inclusion/exclusion criteria; those with estimated GFR lower than 60 mL per minute according to CG and at least one drug prescribed were included for further analysis to determine the appropriateness of dose adjustment. After data collection had been completed, the correctness of the drug dose prescribed for the level of renal function was compared to drug database (Lexi-Comp) available through Up-to-date version 21.2, which can be accessed by searching on any individual drug.

3.3. Populations

- **The source population**: The source populations were all patients visiting the renal clinic of SPHMMC
- **The study population**: were all adult patients visiting the renal clinic of SPHMMC during the study period and have serum creatinine ≥1.2 mg/dL

3.4. Exclusion and inclusion criteria

Inclusion criteria:

- Patients ≥18years of age
- Patients receiving at least one drug and have the most recent SCr≥1.2mg/dL were included

Exclusion criteria

- Patients with the age of less than eighteen years
- Pregnant women
- Patients with acute kidney injury

3.5. Sample size determination and sampling technique

- **Sample size determination**

To determine the required sample size the single population proportion formula was employed; Hence,

$n= (Z_{\alpha/2})^2 pq/d^2$Where: n = sample size

P = percentage

q = 1-p

d = desired degree of precision

Z= is the standard normal value at the level of 95% confidence level

$n= (1.96)^2(0.5X0.5)/ (0.05)^2$ =384, by adding 10% contingency, n=422

- **Sampling techniques**

- Sampling technique was convenience sampling technique in which all patients who visit the renal clinic of SPHMMC and fulfill the inclusion criteria during the study period were included.

- To determine the prevalence of MDRD use by physicians, all physicians working in renal clinic of SPHMMC during the study period were included.

3.6. Study variables

- **Independent variables**

  - Age
  - Sex
  - Scr
  - BSA
  - BMI
  - Weight
  - Co morbidity

- **Dependent Variable**

  - Concordance

3.7. Data collection procedures and analysis

- **Data collection tool**

  Data collection tool was developed based on the variables to be collected and the data were collected from secondary data in individual patient card. Data collection tool (data abstraction format) developed was used to collect individual patient's data including age, sex, Scr, etc. and self administered questionnaire was used to collect data on prevalence of MDRD formula use by physicians

- **Data collectors recruitment**

Two data collectors were recruited from nurses working in Renal Clinic and trained on extraction of data from patient files and techniques of data collection

- **Data quality control**

- To maintain the quality of the data, a data collection checklist was prepared and pretest was done on 5 % of patients for its completeness for coverage of critical domains and wording clarity cross check by randomly selected patients' card. Data collectors were supervised on extraction of data from individual patient's chart regularly

- **Data analysis**

Quantitative raw data collected using secondary data was organized and carried out right after the completion of data collection and data arranged categorically. Then it was entered in to computer, cleaned and analyzed using statistical package for social sciences (SPSS) version 20. Descriptive statistics such as frequencies and percentage was summarized and presented in the form of tables and graphs. Odds ratio and 95% confidence interval was used to check significant association between dependent & independent variables using Bivariate and Multivariate analysis by logistic regression model. Concordance between the two formulas for GFR agreement and dosing recommendation was tested using the kappa test. Pearson's correlation coefficient was calculated to quantify degree of linear relation between CG and MDRD equations. .Bland-Altman analysis was used to show within person difference between the two equations. In all cases, P-value <0.05 was considered to be significant

3.8. Ethical consideration

The letter of ethical approval with a reference number of PCP/449/08/16 was obtained from ethical review board of school of pharmacy, Addis Ababa University and the study was conducted after permission from the Institutional Review Board (IRB) of SPHMMC by obtaining letter of ethical clearance with a reference number PM23/294. Confidentiality of patient data was assured by recruiting data collectors from nurses working in the renal clinic and the name and address of the patient was not recorded on data abstraction format and only patient card was used as identity of the data collected.

4. Result

From a total of 712 patients visited the Renal Clinic of SPHMMC from July - September 2016, 422 patients fulfilled the inclusion criteria and included in the study.

4.1 Socio-demographic characteristics of study participants

Table 2 below shows the socio-demographic characteristics of the study participants. Among the total of 422 patients, 249 (59%) were males. Mean age of patients was 46.09 (SD 15.72). The minimum age was 18 and the maximum was 88. Of the total patients, 289(68.5%) have hypertension as co morbidity followed by diabetes mellitus 115(27.3%), chronic glomerulonephritis 79(18.7%).Of 422 CKD patients 163(38.6%) took at least one drug which needed dose adjustment for the level of renal function. Of this 163 patients, drug dose adjustment was incorrect for 59(35.6 %) according to MDRD formula and 69(42.3%) according to CG formula. Figure 1 shows the frequency of CKD stages among study participants.

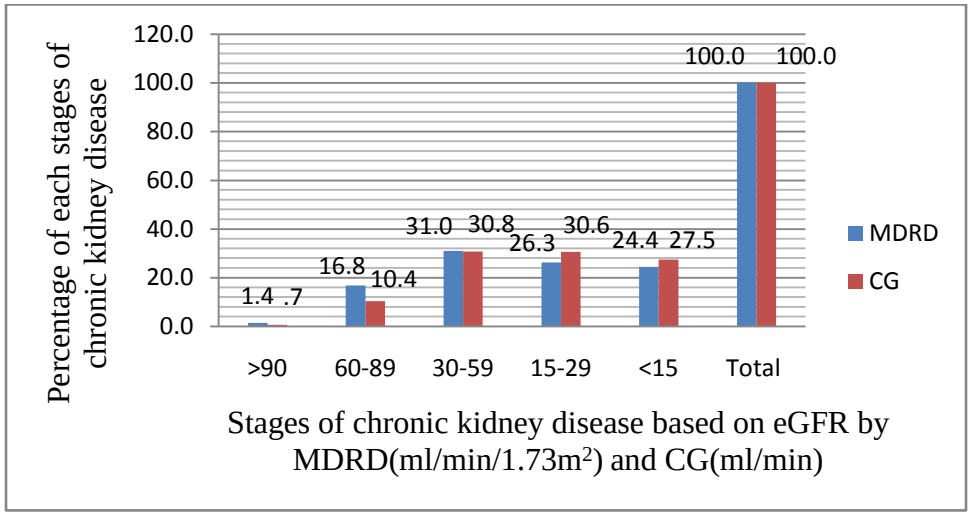

Figure 1: Frequency of chronic kidney disease stages among patients in renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia between July – September, 2016(n=422)

Table 2: Baseline characteristics of chronic kidney disease patients in renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia between July – September, 2016 (n=422)

Variables		N (%)
Age group	<=30	88(20.9)
	31-40	97(23)
	41-50	78(18.5)
	51-60	84(19.9)
	61-70	47(11.1)
	>70	28(6.6)
Sex	Male	249(59)
	Female	173(41)
BMI(Kg/m2)	<18	35(8.3)
	18-24.9	308(73)
	25-30	67(15.9)
	>30	12(2.8)
Cause/Co morbidity	HTN	177(41.9)
	DM	17(4.0)
	CGN	58(13.7)
	Others	55((13)
	HTN,DM,CGN	1(0.2)
	HTN,DM	94(22.3)
	HTN,CGN	17(4.0)
	DM,CGN	3(0.7)
At least one drug need dose adjustment	Yes	163(38.6)
	No	259(61.4)
MDRD correctly adjusted	Yes	105(64.4)
	No	58(35.6)
CG correctly adjusted	Yes	94(57.7)
	No	69(42.3)

HTN=Hypertension;DM=Diabetes Mellitus;CGN=Chronic Glomerulonephritis

4.2 Prevalence of MDRD formula use by physicians working in renal clinic of SPHMMC

Figure 1 below shows prevalence of MDRD formula use by physicians in the renal clinic of SPHMMC during the study period. Of 9 physicians eight physicians used MDRD formula for CKD staging and six physicians used it for drug dose adjustment. Of the eight physicians used MDRD, six of them used BSA unmodified form of MDRD formula.

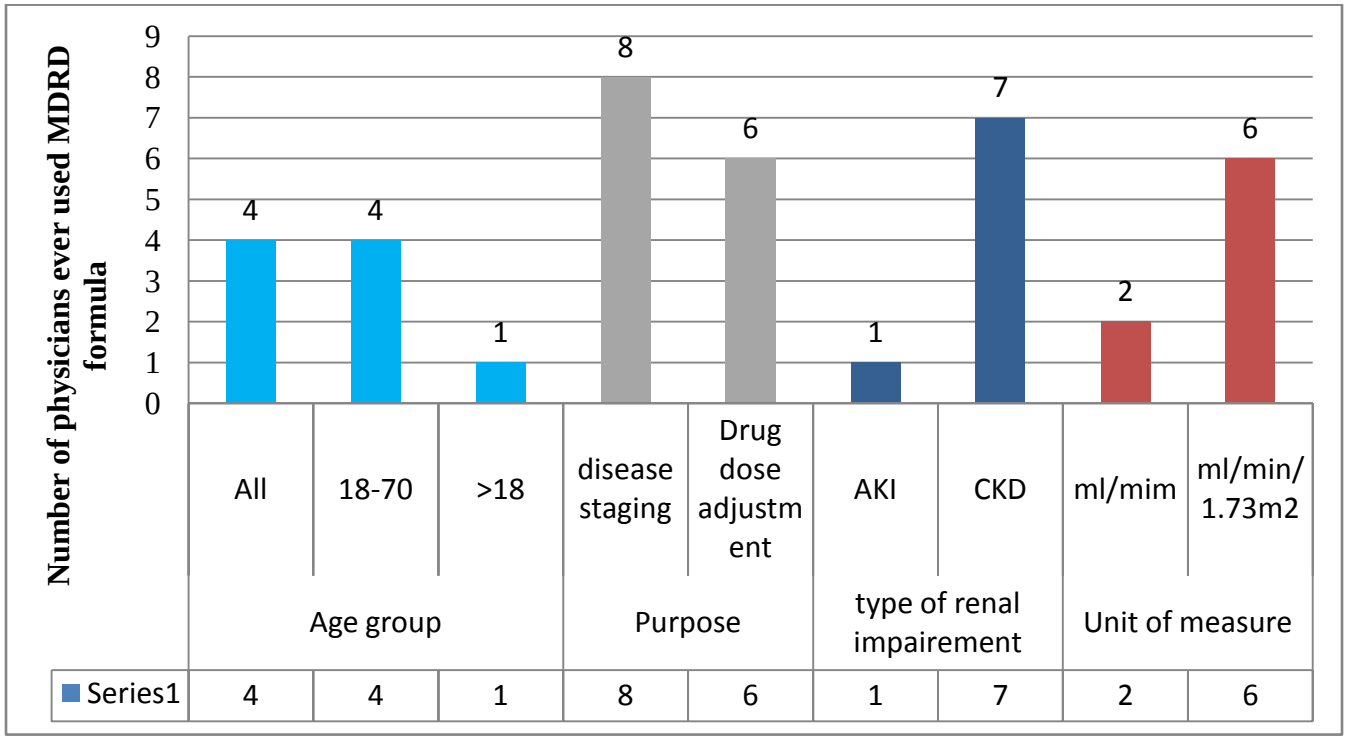

Figure 2: Prevalence of Modification of Diet in Renal Disease formula use by physicians in renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia between July – September, 2016(n=9)

4.3 Correlation between eGFR by Cockcroft-Gault and MDRD formula

As shown in table 3 the Cockcroft-Gault equation correlated best with BSA modified MDRD formula than the BSA unmodified one. The r value was 0.94 with p value of 0.001 for correlation between CG and BSA unmodified MDRD formula. Similarly the CG was correlated to the BSA modified MDRD formula with the r value of 0.97 and p value of 0.001

Table 3: Correlation between CG and MDRD formula in chronic kidney disease patients in renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia between July – September, 2016 (n=422)

Variables	**Mean ± SD**	**R**	**P-value**
MDRD BSA unmodified (ml/min/1.73m^2)	34.76±23.6	0.94	<0.001
CG(ml/min)	30.91±20.69		
MDRD BSA modified(ml/min)	33.80±24.06	0.97	<0.001
CG(ml/min)	30.91±20.69		

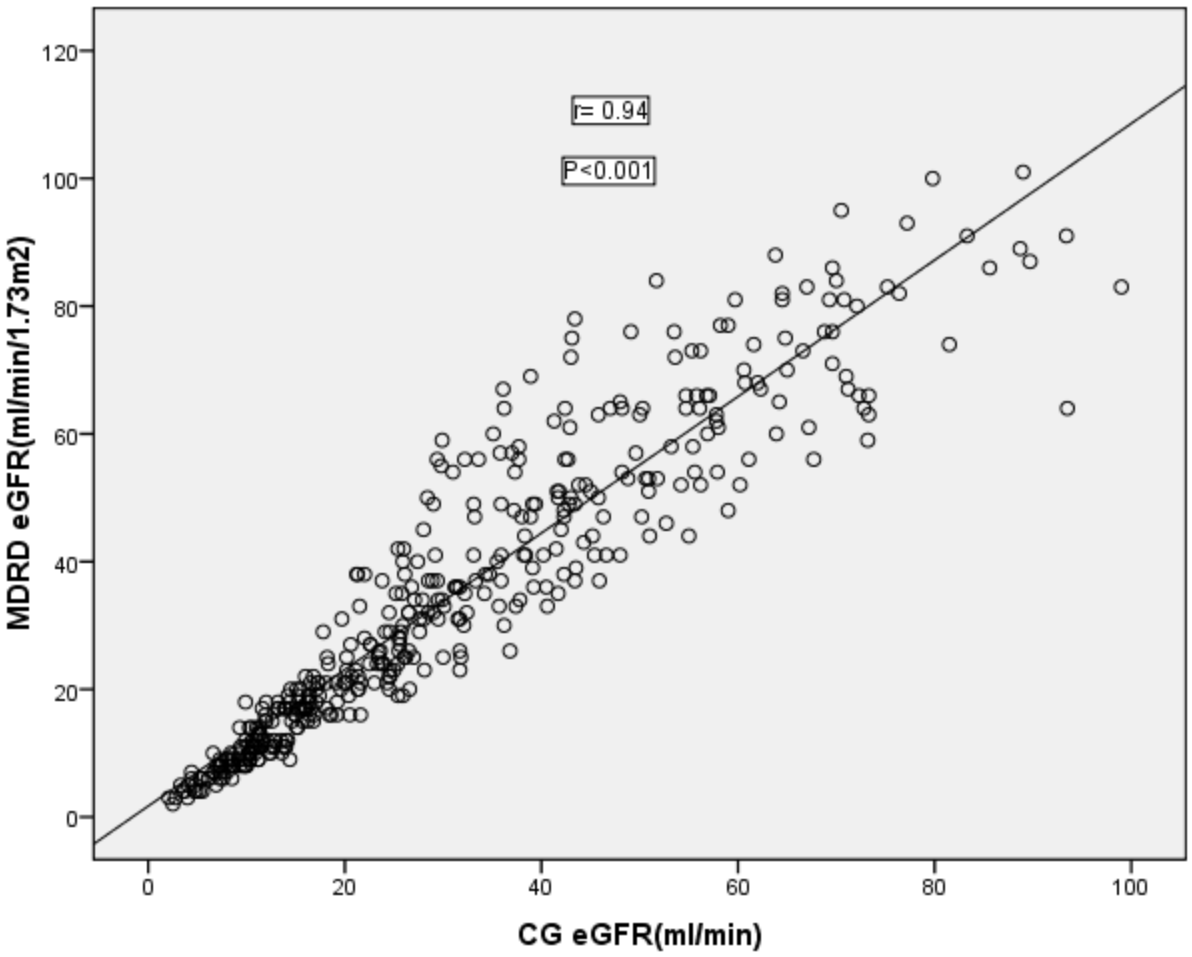

Figure 3: Correlation between estimated glomerular filtration rate by CG and MDRD in chronic kidney disease patients in renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia between July – September, 2016(n=422)

4.4 Concordance between CG and MDRD formula

As shown in table 4 below, concordance of the BSA unmodified MDRD Study equation with CG for FDA assigned kidney function categories was 73.7%% compared to 80.3% for the BSA modified MDRD equation ($p<0.001$). Concordance of BSA unmodified MDRD Study equation with CG for recommended drug dosages was 89.6% compared to 91.4% for BSA modified MDRD equation ($p<0.001$).

Table 4: Concordance between CG and MDRD formula for GFR agreement and drug dosing recommendation in chronic kidney disease patients in renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia between July – September, 2016 (n=422)

		% of agreement	Kappa test	95% CI	P-value
For CKD staging	CG and BSA unmodified MDRD	73.7	0.644	0.58-0.70	.000
	CG and BSA modified MDRD	80.3	0.733	0.68-0.78	.000
For drug dose adjustment	CG and BSA unmodified MDRD	89.6	0.782	0.67-0.87	.000
	CG and BSA modified MDRD	91.4	.820	0.73-0.91	.000

In the current study Bland-Altman analysis was done showing the within person differences between eGFR obtained by CG and MDRD. Agreement of MDRD equation with CG was inspected visually by using Bland-Altman plots and quantified as the 95% limits of agreement between estimates. The limits of agreement represent a range of values within which the true difference between two methods can be said to lie with 95% confidence. In the current study the true difference was between lower 95% CI= -20.19 and upper 95% CI= 12.5 as shown in figure 4 below. MDRD formula overestimates eGFR at lower stages of CKD when compared to CG formula

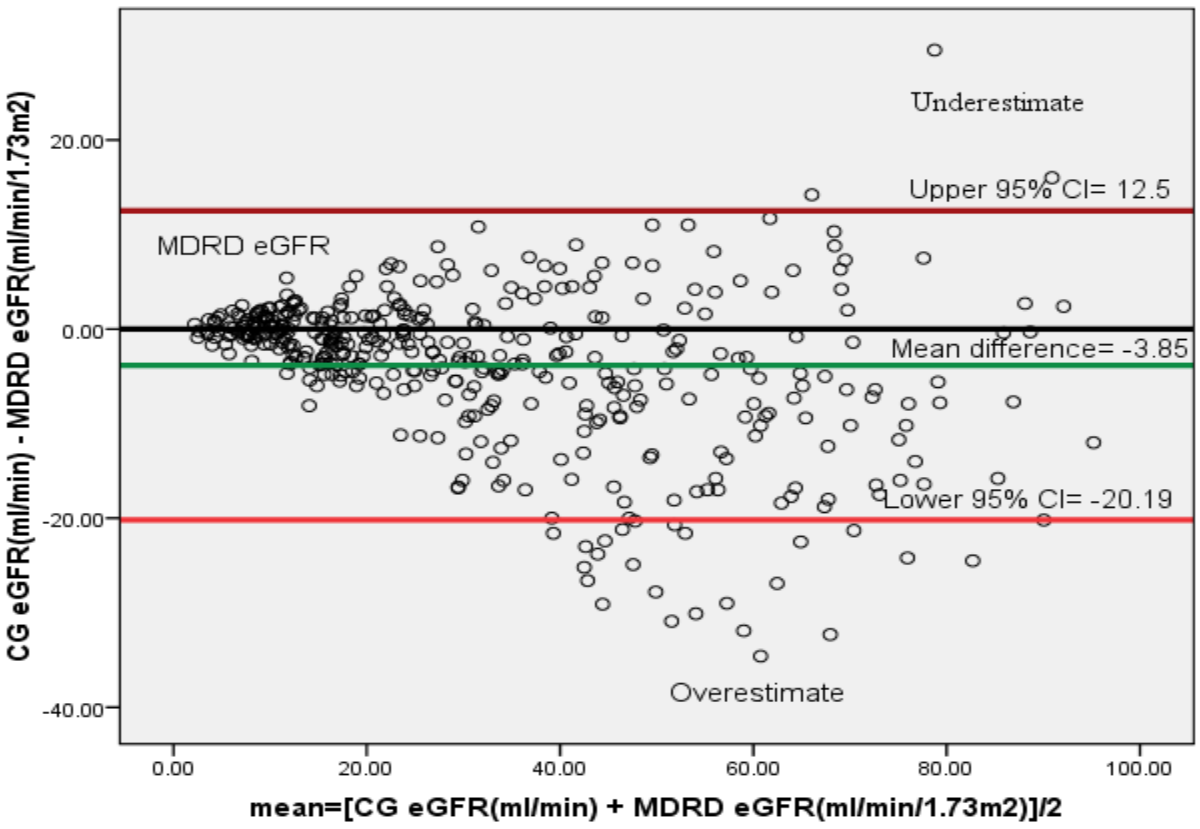

Figure 4: Bland-Altman plots between CG and MDRD formulas in chronic kidney disease patients in renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia between July – September, 2016(n=422)

4.5 Factors associated with concordance between CG and MDRD formula

As shown in table 5 body weight from 61-70 Kg and greater than 70 Kg are associated with concordance between CG and MDRD formula for GFR agreement with 95% CI(0.032-0.803,P=0.026) and 95% CI (0.020,0.621;P=0.012) respectively. Similarly serum creatinine greater than 3.5 mg/dL is associated with higher concordance where as age older than 70 years old is associated with discordance between the two formulas with 95% CI (0.097,0.327)and 95% CI (2.04,15.33;P=0.001) respectively. From table 6, age older than 70 years is associated with

discrepancy between drug dosing recommendation based on CG and MDRD formula with 95% CI (1.22,121.8;P=0.034)

Table 5: Factors associated with the concordance between CG and MDRD formula for GFR agreement in chronic kidney disease patients in renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia between July – September, 2016 (n=422)

Variables		**GFR agreement**		**95% C.I.**		**COR**	**P-value**	**95% C.I.**		**AOR**	**P-value**
		Yes	No	Lower	Upper			Lower	Upper		
Weight(Kg)	≤40	6	8			1					
	41-50	39	27	0.16	1.67	0.52	0.27	0.12	2.15	0.51	0.36
	51-60	110	43	0.10	0.90	0.29	0.03	0.08	1.76	0.39	0.22
	61-70	78	17	0.05	0.53	0.16	0.003	0.03	0.80	0.16	0.03
	>70	78	16	0.05	0.50	0.15	0.002	0.02	0.62	0.11	0.01
Age(years)	≤30	66	22			1					
	31-40	77	20	0.39	1.55	0.78	0.48	0.39	1.78	0.84	0.64
	41-50	61	17	0.41	1.72	0.84	0.63	0.43	2.09	0.94	0.89
	51-60)	60	24	0.61	2.36	1.20	0.60	0.93	4.23	1.99	0.08
	61-70	34	13	0.52	2.56	1.15	0.74	0.67	3.99	1.63	0.28
	>70	13	15	1.43	8.39	3.46	0.01	2.0	15.33	5.59	.001
Sr.Cr(mg/dL)	1.2-3.5	172	92			1					
	>3.5	139	19	0.15	0.44	0.26	.000	0.10	.33	0.18	.000
BMI(Kg/m^2)	<18	15	20			1					
	18-24.9	230	78	0.12	0.52	0.25	.000	0.14	1.02	0.37	0.05
	25-30	58	9	0.04	0.31	0.12	.000	0.08	1.23	0.31	0.10
	>30	8	4	0.10	1.48	0.38	.16	0.13	5.27	0.82	0.83

Table 6: Factors associated with the concordance between CG and MDRD formula for drug dosing recommendation agreement in chronic kidney disease patients in renal clinic of St. Paul's Hospital Millennium Medical College, Addis Ababa, Ethiopia between July – September, 2016 (n=163)

Variables		Drug dose recommendation agreement		95% C.I.		COR	P-value	95% C.I.		AOR	P-value
		Yes	No	Lower	Upper			Lower	Upper		
Sr.Cr(mg/dL)	1.2-3.5	83	15			1					
	>3.5	63	2	0.04	0.8	0.18	0.02	0.04	1.1	0.22	0.06
Age (years)	≤30	28	1			1					
	31-40	30	4	0.39	35.46	3.73	0.25	0.44	42.0	4.32	0.21
	41-50	25	1	0.07	18.86	1.12	0.94	0.07	19.3	1.13	0.93
	51-60)	33	3	0.25	25.86	2.55	0.43	0.32	35.9	3.41	0.31
	61-70	22	3	0.37	39.28	3.82	0.26	0.33	36.6	3.49	0.30
	>70	8	5	1.78	172.17	17.50	0.01	1.22	121.8	12.17	0.03

5. Discussion

This study is a cross sectional survey designed to assess the concordance between MDRD and Cockcroft-Gault formula for CKD staging and for drug dosing recommendations in renal clinic of St. Paul's Hospital Millennium Medical College. In the current study 422 patients were included for the determination of the correlation and concordance between CG and MDRD formula for GFR agreement while only 163(38.6%) patients were analyzed for determining concordance between CG and MDRD formula for drug dosing recommendation because drug dose adjustment was required for the level of renal function in 163 patients. The prevalence of MDRD use among physicians working in renal clinic of SPHMMC was 8 out of nine physicians. Even though there is limited study conducted on physicians' use of MDRD formula; the surveys from College of American Pathologists suggest that 70% of clinical laboratories in the United States were reporting eGFR using the MDRD Study equation (Stevens *et al.*, 2009). The MDRD study equation, which uses age, sex and race (but not weight), along with serum creatinine (SCr), has been more widely utilized in those areas where computerized laboratory estimation of GFR has been advocated, partly due to the fact that weight is not required in its calculation. Similarly, since October 2003, all laboratories in British Columbia report an estimated GFR with every serum creatinine assessment, using the modification of diet in renal disease (MDRD) formula (Gill *et al*., 2007).

Correlation between CG and BSA modified and BSA unmodified MDRD in the current study was r=0.97, p<0.001 and r=0.94, P<0.001 respectively. This is similar with study done by Gill et al in which the correlation of CG and MDRD is very high that is r=0.96 (Gill *et al*., 2007), but the result is greater than what was found by Carmen et al in which the Pearson correlation

coefficient between the CG and the MDRD equations was (0.83, $p < 0.0001$) which is lower than that of current study because the former one used Cockcroft-Gault equation modified for body surface (Caldararu *et al*., 2011).According to Melloni et al correlation between CG and MDRD estimates of GFR was ($r = 0.89$; $p < 0.0001$) and it was conducted on 46,942 patients (Melloni *et al*., 2008).The Pearson's correlation coefficient (95% confidence interval) was 0.84 (0.82-0.85) for Cockcroft-Gault vs. MDRD (Matsha *et al*., 2013). This result is lower than the current study because the former study was community based cohort study which did not restrict the serum creatinine of each participant. The Pearson's correlation coefficient between the GFRs estimated by the Cockcroft-Gault and the MDRD equations in the whole cohort was 0.828 ($p < 0.001$). This is still a lower score than the current study because the former one conducted without regard to the level of serum creatinine of each study participant (Francisco *et al*., 2008). Grillo et al also found that correlation analysis of CG and MDRD estimates shown to be $r^2=0.69$ ($p<0.0001$) which is lower than the current study because the former one included patients' serum creatinine between 0.8 mg/dL and 1.7 mg/dL (Grillo *et al.*, 2010). The Spearman correlation coefficient between measured and estimated GFR for both equations was similar (4-V MDRD r^2 =0.80 and CG r^2 =0.79) but in the current study current study the correlation was done between the MDRD and CG (Deventer *et al.*, 2008).

In the current study concordance between Cockcroft-Gault and BSA unmodified MDRD formula for FDA assigned kidney function categories was 73.7% compared to 80.3% for the BSA modified MDRD equation ($p<0.001$).This result is lower than what was found by Steven et al in which concordance between the MDRD Study equation and the CG for GFR agreement was 78% ($p<0.001$), probably because the latter one used BSA modified MDRD (Stevens *et al*.,

2009).In the current study concordance between CG and MDRD formula for FDA assigned kidney function categories was compromised in under weight, aged population i.e older than 70 years and serum creatinine greater or equal to 1.2 mg/dL and less than 3.5 mg/dL. This result is similar in part with that of Roblin et al, in which most prominent differences were seen in aged and under-weighed subjects (Roblin *et al*., 2009). Park et al also found that using MDRD in place of CG for dosage modification yielded higher dosing recommendations for subjects with a combination of age >80 years, weight <55 kg, and serum creatinine >0.7 and ≤1.5 mg/dL (Park *et al.*, 2012). Another study also found that there is difference between the results given by both MDRD and CG formulas in the elderly over 65 years (P = 0.363) and in Obese subjects (P = 0.142) (Eric *et al*., 2015). However, in the current study obesity was not associated with discordance between CG and MDRD formula rather those patients having body weight less than 61 Kg associated with discrepancy. Another study also found that concordance between CG and MDRD formula was 79%, kappa 0.69 ; 95 CI [0.60-0.77] which is greater than what was found in the current study (Okparavero *et al.*, 2013).Concordance between CG and MDRD for FDA assigned kidney function categories was weak k=0.53, 95%CI [0.47,0.59] (Matsha *et al*., 2013), as compared to the current study which is moderate k=0.644, 95% CI [0.58,0.70].This difference might be due to the fact that the current study was done on patients with renal impairment while the former study was community based. Park et al found that the CG and the MDRD classification of renal function generally agreed (64.2%, κ = 0.54) (Park *et al.*, 2012). MDRD-4 appeared to underestimate the fall in GFR with age compared with creatinine clearance (Ccr) using 24-hour urine collections, CG and CKD-Epi which is similar to the current study in which the major discordance between the MDRD and CG formula is in older poplations (Eastwood *et al*., 2010). Bland-Altman analysis was also carried out in the current study to check whether

there was measurement agreement exist between CG and MDRD formulae or not. As shown from Bland–Altman plots (figure 4), MDRD equation had strong measurement agreement with that of CG at lower eGFR and it become weaker at higher eGFR. MDRD equation overestimates eGFR at lower CKD stages compared to CG. This is similar with what was shown by other studies, in which MDRD overestimates eGFR at higher values (Orvin *et al.*, 2015; Marı *et al.*, 2015). In stage 1–2, CKD eGFR overestimated measured GFR by 52.5, 38.0, and 19.3% for CG, MDRD (ethnicity-corrected), and MDRD (without correction), respectively which is not similar to the current study in which MDRD formula overestimated eGFR at stage 1-2 CKD when compared to CG (Madala *et al.*, 2012).

Concordance of BSA unmodified MDRD Study equation with CG for recommended drug dosages was 89.6% compared to 91.4% for BSA modified MDRD equation ($p<0.001$). This result is similar with stevens et al in which concordance rate between CG and MDRD study equation for recommended drug dosages 89% ($p<0.05$)(Stevens *et al*., 2009). In the current study the discordance rate was 10.4% and it is similar with what was found by Manzano-Fernández et al which was 10% (Manzano-Fernández *et al.*, 2015). Another study also found out the discordance rate between CG and MDRD for drug dosing recommendation to be 12.4% (Moranville and Jennings, 2009). Golik et al conducted comparison of dosing recommendations for four antimicrobial drugs based on CG and MDRD formulas. They found discordance rate ranging from 22.8–36.3% which is different from that of the current study because the former one included only patients' serum creatinine with mean ±SD of 1.41 ± 0.95 mg/dl which contributes to the higher discordance (Golik and Lawrence, 2008).

According to Hermsen et al study, level of concordance for the need for dosage adjustment based on the two equations was moderate (kappa coefficient 0.57, 95% confidence interval 0.5-0.63) (Hermsen *et al.*, 2009) and their result is less than the current study which is good (kappa 0.782, 95% CI 0.67-0.87.).The former study was exclusively done on antimicrobial drugs alone whereas the current study included all drugs which needed drug dose adjustment for the level of renal function which might contribute to the difference between the two studies. In the current study 82.4% of patients with discordant dose recommendation would receive a higher dose if the MDRD GFR was used while 99.1% of patients with discordant dose recommendations would receive a higher dose if the MDRD GFR was used in study done by Hermsen et al (Hermsen*et al*., 2009).Another study also showed that in the 27 discordant cases, 67% of patients would have received a higher dose using the MDRD equation (Sarah *et al*., 2010). In the current study, age >70 years was associated with discordance between the two formulas for drug dosing recommendation. Since implementation of automatic reporting of MDRD calculated GFR in British Columbia, pharmacists have noted large discrepancies in drug doses calculated using MDRD and CG equations in elderly nursing home patients (Gill *et al.*, 2007). Another research also found that those aged ≥80 years were more than 15-fold (OR=15.41; 95% CI 10.00 to 23.75) more likely to be incorrectly dosed by MDRD (MacCallum *et al.*, 2013). For patients with advanced age further work is needed before the MDRD equations can replace the CG equation for dose adjustment in the labeling (Park *et al.*, 2012). According to Mcfarland et al, the greatest discrepancy between CG and BSA modified MDRD for drug dosing recommendation was observed in individuals over 75 years of age. This difference may be because, the latter study used BSA modified MDRD (Mcfarland *et al*, 2012).Another study has also shown that discrepancies between CG and MDRD derived drug dosing regimens have been observed in

elderly patients (Prashanth *et al*., 2016). A Pub Med literature search for all English-language articles published before November 2007 was conducted to compare the use of this estimated GFR with estimated creatinine clearance (CrCl) calculated using the CG equation in the dosing of drugs requiring adjustments in elderly patients with declining renal function. None of the articles identified found that the use of the MDRD equation in the elderly was better than the CG for estimating renal drug elimination (Spruill and Wade, 2008).

6. Limitation of the study

Firstly, this study evaluated recommended doses of various renally excreted dugs rather than outcomes of different dosing. Therefore; outcome were drug dosage recommendations, rather than observed drug efficacy and safety.

The difference in accuracy between CG and MDRD study equation is similar at lower level of GFR. Therefore the reported discordance rates for the MDRD study equation may not accurately reflect discordance at lower GFR where drug dosing adjustment is more common.

Study participants' creatinine levels at the time of study visit were assumed to be at the same levels at the time their drug dosages were determined.

The sample size for physicians for assessing the prevalence of use of Modification of Diet in Renal Disease was too small.

It is not known whether study participants' measured serum creatinine is standardized or not

7. Conclusion

The concordance between CG and MDRD formulas for drug dosing recommendation and for FDA assigned kidney function categories fall into good concordance that is concordance rate 89.6%, kappa= 0.782 and concordance rate 73.7% kappa=0.644 respectively. Age older than 70 years associated with minimal concordance. Therefore; MDRD formula can be used interchangeably with Cockcroft-Gault formula for drug dosing recommendation in all adult patients between the age of 18 and 70 years.

8. Recommendation

Based on the findings of the current study the following recommendations can be made:

- The MDRD formula should not be used for all age groups
- It is important to expand the sample size of Physicians to determine the prevalence of use of MDRD
- The concordance between the CG and MDRD formula for FDA assigned GFR categories should be conducted at community level
- Further research on estimation of GFR and the development of an international consensus on concordant recommendations for practitioners concerning drug dose adjustment in renal failure are desirable

References

Absar Ali, Naila Asif, Z. R. (2013). Estimation of GFR by MDRD Formula and Its Correlation to Cockcroft-Gault Equation in Five Stages of Chronic Kidney Disease. *Journal of Nephrology*, *3*, 37–40.

Addisu, K. S. (2014). Comparison of GFR Estimating Equations with Creatinine Clearance among Patients who Visit Renal Unit of Tikur Anbessa Specialized Hospital. *MSc Thesis in School of Pharmacy, Addis Ababa University*, 68.

Alahdal, A. M., & Elberry, A. A. (2012). Evaluation of applying drug dose adjustment by physicians in patients with renal impairment. *Saudi Pharmaceutical Journal*, *20*(3), 217–220. http://doi.org/10.1016/j.jsps.2011.12.005

Arrabal-durán, P., Durán-garcía, M. E., Ribed-sánchez, A., Hidalgo-collazos, P., & Sanjurjo-sáez, M. (2014). Pharmaceutical interventions in prescriptions for patients admitted with chronic renal failure. *Nefrologia*, *34*(6), 710–715. http://doi.org/10.3265/Nefrologia.pre2014.Jul.12541

Bookstaver, P. B., Johnson, J. W., Mccoy, T. P., Stewart, D., & Williamson, J. C. (2008). Modification of Diet in Renal Disease and Modified Cockcroft- Gault Formulas in Predicting Aminoglycoside Elimination. *The Annals of Pharmacotherapy*, *42*, 1758–1765. http://doi.org/10.1345/aph.1L144

Caldararu, C., Dogaru, M. T., Vari, C. E., & Dogaru, L. G. (2011). Comparison between cockroft-gault and mdrd formula for the estimation of glomerular filtration rate in chronic kidney disease patients. *Farmacia*, *59*(6), 760–769.

Decloedt, E., Leisegang, R., Blockman, M., & Cohen, K. (2010). Dosage adjustment in medical patients with renal impairment at Groote Schuur Hospital. *South Africa Medical Journal*, *100*(5), 304–306.

Devaney, A., & Tomson, C. (2006). Chronic kidney disease — new approaches to classification. *Hospital Pharmacist*, *13*, 406–410.

Deventer, H. E. Van, George, J. A., Paiker, J. E., Becker, P. J., & Katz, I. J. (2008). Estimating Glomerular Filtration Rate in Black South Africans by Use of the Modification of Diet in Renal Disease and Cockcroft-Gault Equations METHODS : RESULTS : *Clinical Chemistry*, *54*(7), 1197–1202. http://doi.org/10.1373/clinchem.2007.099085

Dowling, T. C., Wang, E., Ferrucci, L., & Sorkin, J. D. (2013). Glomerular Filtration Rate Equations Overestimate Creatinine Clearance in Older Individuals Enrolled in the Baltimore Longitudinal Study on Aging : Impact on Renal Drug Dosing. *PHARMACOTHERAPY*, *33*(9), 912–921. http://doi.org/10.1002/phar.1282

Eastwood, J. B., Kerry, S. M., Plange-rhule, J., Micah, F. B., Antwi, S., Boa, F. G., … Cappuccio, F. P. (2010). Assessment of GFR by four methods in adults in Ashanti , Ghana : the need for an eGFR equation for lean African populations. *Nephrol Dial Transplant*, *25*, 2178–2187. http://doi.org/10.1093/ndt/gfp765

Emami, Sepideh Esfahani, H. R., & Farokhi, Farin Rashid Fahimi, F. (2012). Assessment of Drug Dosage Adjustment in Paients with Kidney Disease: Opportuniies for Pharmacist Involvement. *International Journal of Pharmacy and Pharmaceutical Sciences*, *4*(3), 18–21.

Eric, Y. S., Mireille, A., Louis, K. J., Emile, A., Diafouka, F., & Monnet, D. (2015). Glomerular filtration rate of black african people: what concordance between MDRD and Cockroft-gault formulas in old and obese poeple. *Asian Journal of Biochemical and Pharmaceutical Research*, *5*(3), 10–15.

Erler, A., Beyer, M., Petersen, J. J., Saal, K., Rath, T., Rochon, J., … Gerlach, F. M. (2012). How to improve drug dosing for patients with renal impairment in primary care - a cluster-randomized controlled trial. *BMC Family Practice*, *13*(1), 1. http://doi.org/10.1186/1471-2296-13-91

Eun Jung Park, Kunyi Wu, Zenghui Mi, Ting Dong, John P Lawrence, Chia-Wen Ko, Shiew-Mei Huang, Lei Zhang, Victor Crentsil, Jialu Zhang, N. N. X. (2012). A Systematic Comparison of Cockcroft-Gault and Modification of Diet in Renal Disease Equations for Classification of Kidney Dysfunction and Dosage Adjustment. *Annals of Pharmacotherapy*, *46*(9), 1174–1187.

Fanak Fahimi, S. E. and F. R. F. (2012). The Rate of Antibiotic Dosage Adjustment in Renal Dysfunction. *Iranian Journalof Pharmaceutical Research*, *11*(1), 157–161.

Fiseha, T., Kassim, M., & Yemane, T. (2014). Prevalence of chronic kidney disease and associated risk factors among diabetic patients in southern Ethiopia, *2*(4), 216–221. http://doi.org/10.11648/j.ajhr.20140204.28

Franscisco Buitragoa, J. I.. Calvoa, C.. GÓMEZ-Jiméneza, L.. Cañóna, N. R.. Roblesb, E. .

Angulo. (2008). Comparison and agreement of the Cockcroft-Gault and MDRD equations to estimate glomerular filtration rate in diagnosis of occult chronic kidney disease. *Nefrologia*, *28*(3), 301–10.

Getachew, H., Tadesse, Y., & Shibeshi, W. (2015). Drug dosage adjustment in hospitalized patients with renal impairment at Tikur Anbessa. *BMC Nephrology*, *16*(158), 1–9. http://doi.org/10.1186/s12882-015-0155-9

Gidey, K., Gebre-samuel, N., Molla, F., Abrha, S., Wondimu, A., Assen, A., … Pattnaik, G. (2015). Drug Dose Adjustment Practices in Patients with Renal Impairment at Ayder Referral Hospital, Mekelle, Northern Ethiopia. *International Journal of Pharmaceutical Sciences Review and Research*, *30*(2), 153–157.

Gill, J., Malyuk, R., Djurdjev, O., & Levin, A. (2007). Use of GFR equations to adjust drug doses in an elderly multi-ethnic group - A cautionary tale. *Nephrology Dialysis Transplantation*, *22*(10), 2894–2899. http://doi.org/10.1093/ndt/gfm289

Hartmann, B., Czock, D., & Keller, F. (2010). Drug Therapy in Patients With Chronic Renal Failure. *Dtsch Arztebl Int*, *107*(37), 647–56. http://doi.org/10.3238/arztebl.2010.0647

Hassan, Y., Pharm, D., Al-ramahi, R. J., Aziz, N. A., Pharm, D., & Ghazali, R. (2009). Drug Use and Dosing in Chronic Kidney Disease. *Annals Academy of Medicine*, *38*(12), 1095–1103.

Heather A Nyman, Thomas C Dowling, Joanna Q Hudson, Wendy L St Peter, Melanie S Joy, T. D. N. (2011). Comparative Evaluation of the Cockcroft-Gault Equation and the Modification of Diet in Renal Disease (MDRD) Study Equation for Drug Dosing: An Opinion of the Nephrology Practice and Research Network of the American College of Clinical Pharmacy. *Pharmacotherapy*, *31*(11), 1130–44.

Hermsen ED, Maiefski M, Florescu MC, Qiu F, R. M. (2009). Comparison of the Modification of Diet in Renal Disease and Cockcroft-Gault equations for dosing antimicrobials. *Pharmacotherapy*, *29*(6), 649–655.

Iskandar, H., Hidayat, W. U., & Hersunaryati, Y. (2012). A Rerospective Study on the Potential Drug Interactions between Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Antagonist and Other Drugs in End-stage Chronic Renal Failure. *International Research Journal of Pharmacy*, *3*(10), 86–89.

J. A. Grillo, S. Abraham, A. Khandelwal, Q. Liu, B. Booth, N. A. Rahman, S. S. (2010). A comparison of the Cockroft-Gault (CG) and the modification of diet in renal disease

(MDRD) equations for estimating renal function and guiding dose adjustment of oncology-related drugs. *Journal of Clinical Oncology*, *28*(15).

Jessica Parsh, Milan Seth, Herbert Aronow, Simon Dixon, Michael Heung, Roxana Mehran, H. S. G. (2015). Choice of Estimated Glomerular Filtration Rate Equation Impacts Drug-Dosing Recommendations and Risk Stratification in Patients With Chronic Kidney Disease Undergoing Percutaneous Coronary Interventions. *Journal of American College of Cardiology*, *65*(25), 2714–2723.

Karsch-völk, M., Schmid, E., Wagenpfeil, S., & Linde, K. (2013). Kidney function and clinical recommendations of drug dose adjustment in geriatric patients. *Karsch-Völk et Al. BMC Geriatrics*, *13*(92), 1–27.

KDIGO. (2013). KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Official Journal of the International Society of Nephrology*, *3*(1).

Kondo, Y., Ishitsuka, Y., Shigemori, E., Irikura, M., Kadowaki, D., Hirata, S., … Irie, T. (2014). Awareness and current implementation of drug dosage adjustment by pharmacists in patients with chronic kidney disease in Japan : a web-based survey. *BMC Health Services Research*, *14*(615), 1–8. http://doi.org/10.1186/s12913-014-0615-0

Leendertse, A. J., Dijk, E. A. Van, Smet, P. A. G. M. De, Egberts, T. C. G., & Bemt, P. M. L. A. Van Den. (2012). Contribution of Renal Impairment to Potentially Preventable Medication-Related Hospital Admissions. *Annals of Pharmacotherapy*, *46*, 625–633. http://doi.org/10.1345/aph.1Q633

Levey, A. S., Bosch, J. P., Lewis, J. B., Greene, T., Rogers, N., & Roth, D. (1999). A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. *Annals of Internal Medicine*, *130*(6), 461–70. http://doi.org/199903160-00002 [pii]

Long CL, Raebel MA, Price DW, M. D. (2004). Compliance with dosing guidelines in patients with chronic kidney disease. *Annals of Pharmacotherapy*, *38*(5), 853–8.

Madala, N. D., Nkwanyana, N., Dubula, T., & Naiker, I. P. (2012). Predictive performance of eGFR equations in South Africans of African and Indian ancestry compared with 99mTc-DTPA imaging. *International Urology and Nephrology*, *44*(3), 847–855.

Marı, F., Orenes-pin, E., Manzano-ferna, S., Vicente, V., Lip, G. Y. H., & Rolda, V. (2015).

Comparison of Estimated Glomerular Filtration Rate Equations for Dosing New Oral Anticoagulants in Patients With Atrial Fibrillation. *Rev Esp Cardiol.*, *68*(6), 497–504.

Matsha, T. E., Yako, Y. Y., Rensburg, M. A., Hassan, M. S., Kengne, A. P., & Erasmus, R. T. (2013). Chronic kidney diseases in mixed ancestry south African populations : prevalence , determinants and concordance between kidney function estimators. *BMC Nephrology*, *14*(1), 1. http://doi.org/10.1186/1471-2369-14-75

Matzke, G. R., Aronoff, G. R., Jr, A. J. A., Bennett, W. M., Decker, B. S., Eckardt, K., … Sica, D. A. (2011). Drug dosing consideration in patients with acute and chronic kidney disease — a clinical update from Kidney Disease : Improving Global Outcomes (KDIGO). *Kidney International*, *80*(11), 1122–1137. http://doi.org/10.1038/ki.2011.322

Mcfarland, M. S., Markley, B. M., Zhang, P., & Hudson, J. Q. (2012). Evaluation of Modification of Diet in Renal Disease study and Cockcroft-Gault equations for sitagliptin dosing. *JNEPHROL*, *25*(04), 515–522. http://doi.org/10.5301/jn.5000026

Melloni, C., Peterson, E. D., Chen, A. Y., Szczech, L. A., Newby, L. K., Harrington, R. A., … Alexander, K. P. (2008). Cockcroft-Gault Versus Modification of Diet in Renal Disease Importance of Glomerular Filtration Rate Formula for Classification of Chronic Kidney Disease in Patients With Non – ST-Segment Elevation Acute Coronary Syndromes. *Journal of the American College of Cardiology*, *51*(10), 991–996. http://doi.org/10.1016/j.jacc.2007.11.045

Melloni, C., Peterson, E. D., Chen, A. Y., Szczech, L. a., Newby, L. K., Harrington, R. a., … Alexander, K. P. (2008). Cockcroft-Gault Versus Modification of Diet in Renal Disease. Importance of Glomerular Filtration Rate Formula for Classification of Chronic Kidney Disease in Patients With Non-ST-Segment Elevation Acute Coronary Syndromes. *Journal of the American College of Cardiology*, *51*(10), 991–996. http://doi.org/10.1016/j.jacc.2007.11.045

Michael P Moranville, H. R. J. (2009). Implications of using modification of diet in renal disease versus Cockcroft–Gault equations for renal dosing adjustments. *American Journal of Health System Pharmacy*, *66*(2), 154–61.

Monica V Golik, K. R. L. (2008). Comparison of Dosing Recommendations for Antimicrobial Drugs Based on Two Methods for Assessing Kidney Function: Cockcroft-Gault and Modification of Diet in Renal Disease. *Pharmacotherapy*, *28*(9), 1125–32.

Myrna Y. Munar, H. S. (2007). Drug Dosing Adjustments in Patients with Chronic Kidney Disease. *American Family Physician*, *75*(10).

Narva, A. S. (2009). Assessment of Kidney Function for Drug Dosing. *Clinical Chemistry*, *55*(9), 1609–1611. http://doi.org/10.1373/clinchem.2009.127944

Nathan R. Hill, Samuel T. Fatoba, Jason L. Oke, Jennifer A. Hirst, C., & A. O'Callaghan, Daniel S. Lasserson, F. D. R. H. (2016). Global Prevalence of Chronic Kidney Disease– A Systematic Review and Meta-Analysis. *PLoS ONE*, *11*(7), e0158765.

Nielsen, A. L., Henriksen, D. P., Marinakis, C., Hellebek, A., Birn, H., Nybo, M., … Pedersen, C. (2014). Drug Dosing in Patients with Renal Insufficiency in a Hospital Setting using Electronic Prescribing and Automated Reporting of Estimated Glomerular Filtration Rate. *Basic and Clinical Pharmacology and Toxicology*, *114*, 407–413. http://doi.org/10.1111/bcpt.12185

Nugent, R. A., Fathima, F., & Feigl, A. B. (2011). The Burden of Chronic Kidney Disease on Developing Nations : A 21st Century. *Nephron Clin Pract*, *118*, 269–277. http://doi.org/10.1159/000321382

Okparavero, A. A., Tighiouart, H., Krishnasami, Z., Wyatt, C. M., Graham, H., Hellinger, J., & Inker, L. A. (2013). Original article Use of glomerular filtration rate estimating equations for drug dosing in HIV-positive patients. *Antiviral Therapy*, *18*, 793–802. http://doi.org/10.3851/IMP2676

Orvin, K., Eisen, A., Goldenberg, I., Shlomo, N., & Gevrielov-yusim, N. (2015). The proxy of renal function that most accurately predicts short- and long-term outcome after acute coronary syndrome. *American Heart Journal*, *169*(5), 702–712. http://doi.org/10.1016/j.ahj.2015.01.012

Ospedaliere, A., Riuniti, O., & Negri, M. (2005). Chronic renal diseases as a public health problem : Epidemiology , social , and economic implications. *Kidney International*, *68*(98), 7–10.

Pedone C, Corsonello A, I. R. (2006). Estimating renal function in older people: a comparison of three formulas. *Age Ageing*, *35*, 121–126.

Peter K MacCallum, Rohini Mathur, Sally A Hull, Khalid Saja, Laura Green, Joan K Morris, N. A. (2013). Patient safety and estimation of renal function in patients prescribed new oral anticoagulants for stroke prevention in atrial fibrillation: a cross-sectional study. *British*

Medical Journal, *3*(9).

Prajapati, A and Ganguly, B. (2013). Appropriateness of drug dose and frequency in patients with renal dysfunction in a tertiary care hospital. *Journal of Pharmaceutical and Biological Sciences*, *5*, 136–40.

Prashanth Rajagopalan, Georgi Abraham, Yuvaram NV Reddy, Ravivarman Lakshmanasami, ML Prakash, and Y. N. R. (2016). Population-based estimation of renal function in healthy young Indian adults based on body mass index and sex correlating renal volume, serum creatinine, and cystatin C. *Int J Nephrol Renovasc Dis.*, *9*, 243–247.

Roblin, I., De Sobarnitsky, S., Basselin, C., Vial, F., Bard, E., Dufrene, I., … Laurencin, C. (2009). Estimated glomerular filtration rate for drug dose adjustment: Cockcroft and Gault or abbreviated MDRD equation? *Clinical Biochemistry*, *42*(1-2), 111–113. http://doi.org/10.1016/j.clinbiochem.2008.09.110

Rothenbacher, Q.-L. Z. and D. (2008). Prevalence of chronic kidney disease in population-based studies: Systematic review. *BMC Public Health*, *8*(117), 1–17.

Salomon, L., Deray, G., Jaudon, M. C., Chebassier, C., & Bossi, P. (2003). Medication misuse in hospitalized patients with renal impairment. *International Journal for Quality in Health Care*, *15*(4), 331–335.

Sarah Jennings, Mario L De Lemos, Adeera Levin, N. M. (2010). Evaluation of creatinine-based formulas in dosing adjustment of cancer drugs other than carboplatin. *Journal of Oncology Pharmacy Practice*, *16*(2), 113–9.

Sergio Manzano-Fernández , José M. Andreu-Cayuelas , Francisco Marín , Esteban Orenes-Piñero , Pilar Gallegob, Mariano Valdés , Vicente Vicente , Gregory Y.H. Lip, V. R. (2015). Comparison of Estimated Glomerular Filtration Rate Equations for Dosing New Oral Anticoagulants in Patients With Atrial Fibrillation. *Rev Esp Cardiol.*, *68*(6), 497–504.

Stanifer, J. W., Jing, B., Tolan, S., Helmke, N., Mukerjee, R., Naicker, S., & Patel, U. (2014). The epidemiology of chronic kidney disease in sub-Saharan Africa : a systematic review and meta-analysis. *The Lancet Global Health*, *2*(3), 174–181. http://doi.org/10.1016/S2214-109X(14)70002-6

Stevens, L. A., Nolin, T. D., Richardson, M. M., Feldman, H. I., Lewis, J. B., Rodby, R., … Zhang, Y. L. (2009). Comparison of Drug Dosing Recommendations Based on Measured GFR and Kidney Function Estimating Equations. *American Journal of Kidney Diseases*,

54(1), 33–42. http://doi.org/10.1053/j.ajkd.2009.03.008.Comparison

Sunder, S., Jayaraman, R., Mahapatra, H. S., Sathi, S., Ramanan, V., & Kanchi, P. (2014). Estimation of renal function in the intensive care unit : the covert concepts brought to light. *Journal of Intensive Care*, *2*(1), 1–7. http://doi.org/10.1186/2052-0492-2-31

Turner, N. (2016). *Oxford Textbook of Clinical Nephrology* (fourth edi). Oxford: Oxford, United Kingdom:Oxford University Press, 2016.

William J. Spruill, W. E. W. (2008). Comparison of estimated glomerular filtration rate with estimated creatinine clearance in the dosing of drugs requiring adjustments in elderly patients with declining renal function. *The American Journal of Geriatric Pharmacotherapy*, *6*(3), 153–160.

Annex I. Questionnaires

1. Demographic information

   Age: _____

   Sex: _____

   Specialty:

   Specialist ☐

   Resident ☐

   General practitioner ☐

2. Have you ever used GFR estimating equation(s)?

   Yes ☐ No ☐ If No, thank you.

3. If yes which one and for what purpose? You can choose more than one alternatives

a. Cockcroft-gault : For estimating GFR ☐ For drug dose adjustment ☐ For both ☐
b. MDRD : For estimating GFR ☐ For drug dose adjustment ☐ For both ☐
c. Others specify:

4. If your choice for question 3, is "B" and used it for drug dose adjustment, for which patient group?

a. Age>70 years
b. Age 18-70 years
c. Age<18 years
d. All age groups

5. Again if your choice for question 3, is "B" and used it for drug dose adjustment, for which type of renal impairment?

   A. AKI

   B. CKD

6. Which unit do you use for MDRD formula in drug dose adjustment?

   A. ml/min B.ml/min/1.73 m^2

Annex II: Data abstraction format

1. Card No:_____
2. Sex: Male ☐ Female: ☐
3. Age:_____years
4. Weight:_____Kg
5. Height:_____cm
6. Date of hospital visit:_____
7. Reason of Hospital visit:_____
8. Lab Findings:

Scr (mg/dL)	BUN(mg/dL)	Date of measurement

9. List of drug prescribed during visit or Hospital stay

S.N	Drug prescribed	Dose, frequency, administration, duration	Date prescribed
1			
2			
3			
4			
5			
6			
7			
8			
9			
10			

10. Known Cause/Co morbid diseases:

1. Hypertension
2. Diabetes mellitus
3. Glomerulonephritis
4. Others specify: _____

Annex III-Consent Form

Addis Ababa University

College of Health Science

Post Graduate Studies

School of Pharmacy

Department of Pharmacology and clinical pharmacy

Informed consent form prepared to compare MDRD equation with Cockcroftgault among patients who visit renal unit of St. Paul's Hospital Millennium Medical College.

Part I: Information about the Study

My name is Hunduma Dinsa Ayeno; currently I am a graduate student at the department of Pharmacology and Clinical Pharmacy, College of health science, Addis Ababa University. I am conducting a study entitled "Concordance between Modification of Diet in Renal Disease and Cockcroft-Gault formulas in chronic kidney disease patients at St. Paul's Hospital Millennium Medical College". If you participate in the study, it is important to know the prevalence of use of the MDRD formula for dosing recommendation. Furthermore, the result of this research is important to identify the degree of the agreement between the MDRD formula and Cockcroft-Gault formulas for drug dosing recommendations. The information which obtained from the study will also contribute for determining if Cockcroft-Gault equation might be replaced by the abbreviated MDRD equation for dosage adjustment in chronic kidney disease patients. I kindly request you to participate in this study by providing response for all the following questions. This information will be used only for research purpose. Your participation in this study is completely on voluntary bases and you have a right to refuse or interrupt the participation at any time. You will not write your name on the questionnaires. Your genuine participation is very important for the outcome of the research and all of your information is kept confidentially. If you need clarification you can ask questions .I would like to appreciate your participation.

Part II consent

Are you volunteer to participate in the study 1. Yes _____ 2.No_____

In signing this document, I am giving my informed consent to participate in the study entitled "Concordance between Modification of Diet in Renal Disease and Cockcroft-Gault formulas in chronic kidney disease patients at St. Paul's Hospital Millennium Medical College". I have been informed that the purpose of this research. I have been informed that my participation in this study is willing full and voluntary even. I have right to refuse or interrupt from participating in the study any time and my name will not be mentioned on the questionnaire. I undersigned, have understood the purpose of the study and fully agreed to participate in the study.

Participant's

Name _____ Signature _____ Date _____

Data Collector's

Name _____ Signature _____ Date _____

Supervisor's

Name _____ Signature _____ Date _____