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DEPARTMENT OF MEDICAL BIOCHEMISTRY

ASSESSMENT OF SERUM ELECTROLYTE LEVEL AND KIDNEY FUNCTION TESTS AMONG ETHIOPIAN PUBLIC HEALTH INSTITUTE STAFF MEMBERS: A CROSS SECTIONAL STUDY.

BY

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This is to certify that the work described in this thesis entitled; Assessment of serum electrolyte level and kidney function tests among Ethiopian Public Health Institute Staff Members: a cross sectional study. It is submitted in partial fulfillment of the requirements for the degree of Master of Science in Medical Biochemistry complies with regulations of the Addis Ababa University.

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Abstract

Background: Chronic kidney disease (CKD) becomes one of the public health problems and major cause of mortality because of late diagnosis that makes it difficult to treat and prevent the adverse outcomes. CKD is asymptomatic until end stage. Early screening, detection, and identification of kidney disease or risk groups are based on laboratory findings. In developing country including Ethiopia screening is very rare and currently, hearing sudden death from kidney failure and its complication is increasingly becoming common.

Objectives: The objective of this study was screening and early detection of chronic kidney disease (CKD) by assessing serum electrolytes and kidney function tests and to detect the associated risk factors for CKD among Ethiopian Public Health Institute (EPHI) Staff Members

Methodology: Cross sectional based study was conducted using WHO stepwise survey among volunteers of EPHI staff members. Automated COBAS 6000 Analyzer was used to analyze the samples. Statistical data analysis was held by SPSS version 20 model and the association of risk factors with the prevalence of CKD was assessed using logistic regression. Data was collected by senior health professionals. Blood sample collection was done through standardized, calibrated, and sterile technique by laboratory technologist. Ethical clearance was obtained from Ethiopian Public Health Institute- Institutional Review Board (EPHI-IRB) and Addis Ababa University Biochemistry Department Ethics and Research Committee (DRERC).

Results: Total of 412 study participants were screened in this study. About 51.2% were males and the majority of the study participants (41%) were between ages of 18-32 years. Most study participants (60%) were married. Alcohol drinking (66%) was the most common bad behavioral practice. None of these study participants showed chronic kidney disease. But about 3.6% by MDRD and 1.9% by CKD-EPI equations were in stage two kidney disease. Self-reported previous history of hypertension, diabetes, and CVD, obesity, and family history of kidney failure were common in the study participants which comprise 18%, 3.4%, 5.3%, 8.5%, and 6.1% respectively. Hyperkalemia (9.5%) and hypocalcemia (8.5%) were the most common electrolyte disorders. Hyponatremia and hypophosphatemia were not found.

Conclusion: The prevalence of stage two kidney disease was relatively low and no one was under serious kidney disease (GFR <60mmoL/min/1.73m^2). Older age, high BMI, and previous history of CVD were significantly associated factors for reduced glomerular filtration rate.

Key words: Prevalence, screening, GFR, CKD, and risk factors.

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Table of Contents

List of figures

List of tables

Acronyms and Abbreviations

NCDs	Non communicable diseases
GBD	Global burden of disease
CKD	Chronic kidney diseases
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
ESRD	End-stage renal disease
C-G	Cock croft – Gault equation
MDRD	Modification of Diet in Renal Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
KDIGO	kidney disease improving global outcome
RAAS	Renin angiotensin aldosterone system
CVD	Cardiovascular disease
WHO	World health organization
PTH	Parathyroid hormone
CKD-MBD	Chronic kidney disease related mineral bone disorder
BMI	Body mass index
SLC6A8	Solute carrier family 6, member 8
EPHI	Ethiopian public health institute
EPHI-IRB	EPHI Institutional review board
DRERC	Biochemistry Department Ethics and Research committee
EGTA	Ethylene glycol tetra acetic Acid
EDTA	ethylene di amine tetra acetic acid
NM-BAPTA	5-nitro-5'-methyl-(1, 2-bis (o-amino phenoxy) ethan N,N,N',N'-tetra acetic acid

1. INTRODUCTION

Non communicable diseases (NCDs) gets global attention because of their rapid increasing rate, they become the major causes of morbidity and mortality world widely (Lozano *et al.*, 2012). According to 2016 global burden of disease (GBD) report 72.3% of the total death from 2006-2016 is caused by NCDs with increasing trend year by year (Steel, 2017). NCD includes cardiovascular disease, diabetes mellitus, cancer, chronic kidney diseases, and chronic respiratory diseases. Cardiovascular disease is the leading cause of death followed by cancer among NCDs according to 2016 GBD report (Steel, 2017). Chronic kidney diseases (CKD) is also a major cause of mortality because of lack of early screening and detection of the disease and its asymptomatic nature, as result of this, CKD becomes one of the public health problem. (Stevens *et al*., 2006; Elhafeez *et al*., 2018). The global prevalence of CKD in 2016 is estimated between 11 to 13% at which the majority is stage three with rapid increasing rate in the developing countries (Hill *et al.*, 2016).

Chronic kidney disease is one of the commonest chronic disorders that is characterized by structural or functional abnormalities of the kidney with or without a decrease in glomerular filtration rate (GFR less than 60 mL per minute per 1.73m^2 of body surface area for minimum of three months) (Levey *et al.*, 2003, Levey *et al*., 2002, Baumgarten and Gehr, 2011). CKD is more prevalent than end-stage renal disease (ESRD) with increasing rate over time and early detection and treatment of CKD is very important to delay ESRD occurrence (Snyder and Pendergraph, 2005). The main obstacle of CKD in the general population is lack of symptoms until end-stage renal disease (Baumgarten and Gehr, 2011). Hematuria and other non-specific urinary tract symptoms may be manifested in some patients with CKD. Electrolyte derangement with abnormal renal function tests are the common laboratory finding (Webster *et al.*, 2017). Estimated GFR (eGFR) is regarded as a good laboratory tool to show abnormality of kidney function that can be calculated from serum creatinine level (Levin *et al*., 2013).

There are many risk factors for the development and progression of CKD, but the most common are hypertension, diabetes, first relative family history of CKD, obesity, and older age, which contribute for the majority of CKD development (Hogg *et al.*, 2003, Levey *et al.*, 2005). Globally, diabetes and hypertension are cause of more than two-third of CKD (Chen *et al.*, 2006). The other risk factors for the development of CKD are autoimmune disorder, exposure to

certain chemicals and drugs (like lead, arsenic, acyclovir, aminoglycosides, amphotericin B, and vancomycin), low income, low educational level, urinary tract infections, systemic infections, lower urinary tract obstruction, neoplasia, recovery from acute kidney injury, and reduction in kidney mass (Baumgarten and Gehr, 2011).

The seriousness of CKD is diagnosis at end stage, which is harsh, disabling, and even fatal. In addition untreated CKD is one of the major risk factor to increase the progression, mortality rate, and adverse outcome of cardiac diseases like myocardial infarction, and stroke (Dries *et al.*, 2000, Fried *et al.*, 2003, Manjunath *et al.*, 2003, Lindner *et al.*, 2007). To solve this big problem researchers are advised to screen and treat CKD at early stage especially those who are at high risk, but in low and middle income countries including Ethiopia early CKD screening is very rare and sudden hearing of renal failure becomes common. This study aims to assess and screen the kidney function status by measuring the level of some electrolytes in the serum and renal function tests to detect early CKD among the volunteers of Ethiopian public health institute staff members.

1.1. Literature reviews

1.1.1. Chronic kidney disease (CKD)

CKD is a syndrome that arises from different heterogeneous disease that is characterized by persistent occurrence of functional and/ or structural abnormality of the kidney usually for more than three months (Levin *et al.*, 2013, Webster *et al.*, 2017). Kidney dysfunction can be predictable by increased serum levels of creatinine, cystatin C, blood urea nitrogen and structural abnormality of the kidney, usually identified by imaging (Romagnani *et al.*, 2017). In addition proteinuria is an important marker for the detection of kidney damage. 2013 international guideline of CKD defines, CKD as the presence of reduced kidney function detected by GFR < 60 mL/min per 1·73 m^2 with or without kidney damage detected by kidney damage biomarkers that persist for at least three months regardless of clinical diagnosis and the underline causes (Levin *et al.*, 2013).

Kidney function can be detected by deferent investigations, but the most important and good indicator of functional abnormality is GFR, which is an indicator of all functional nephrons that filtered the total amount of fluids per unit of time (Levey *et al.*, 2015). This is because, one of the

main function of kidney is filtration of the waste materials in the fluids and bloods to reabsorb the metabolically important materials as well as to remove the waste and toxic substances, but during renal failure waste products are unable to remove completely, which will cause further damage of the vital organs in the body (Small *et al.*, 2012). Nephron is the smallest functional unit of kidney that composed of glomerulus and renal tubule. Each kidney contains more than one million nephrons and each nephron comprises a single glomerulus (Pollak *et al.*, 2014).

Glomeruli are the site for the first step of urine formation through the filtration of water in the plasma. Each nephron yields around 100 µL of ultra-filtrate per day. GFR is defined as the rate of ultra-filtration gained by the summation of the single filtration rates around 2 million glomeruli in two kidney, which can be approximately 120 - 140 mL/min/1.73m^{2}of body surface area in healthy adults and can be gradually decreased after 30 years old without any pathogenic disorders of the kidney (Baumgarten and Gehr, 2011, Pollak *et al*., 2014). GFR less than 60 mL/min/1.73m^2 with/without the marker of kidney damage is diagnosed as CKD, which is the main indicator of renal function reduction or impairment (Levin *et al*., 2013).

The physiological function of kidney can be grouped into homoeostasis, endocrine activity, and excretion. The homoeostatic activities of kidney are blood volume regulation, acid/base balance (pH) regulation, and maintenance of different electrolyte levels. The endocrine activity of kidney is the production of renin and erythropoietin that involve in blood pressure regulation and red blood cell production respectively. Vitamin D metabolism is also regulated by kidney. In addition to this kidney is the main organ that removes the toxic waste substances like creatinine and urea through urine (Gowda *et al*., 2010).

The functional status of kidney can be detected by measuring the level of creatinine, blood urea nitrogen, serum electrolyte, GFR, and red blood cell profiles (Gowda *et al.*, 2010). The frequently requested kidney function test to diagnosis CKD is GFR (Stevens *et al.*, 2006). GFR measures the clearance of the substance that passes through kidney for excretion after glomerular filtration. Measuring the rate of inulin GFR is the gold standard because inulin passes through the kidney without any change, but it has very complex procedure (Snyder and Pendergraph, 2005). Creatinine clearance by taking 24 hour urine can also be used to estimate GFR, but it is time consuming, needs accurate urine collection and can also result over estimation of GFR because kidney can actively secrete creatinine and muscle mass can also influence the GFR

(Baumgarten and Gehr, 2011). To overcome this problem researchers are advised to calculate the eGFR by taking serum creatinine levels and other variables that affect the relationship between creatinine and GFR including age and sex (Levey *et al.*, 1999).

In 1926, Rehberg develops the first estimation of GFR by using creatinine through the administration of the exogenous creatinine (Rehberg, 1926) and in 1937, Popper and Mandel develops estimation of GFR by using the endogenous creatinine clearance (Popper and Mandel, 1937). The researchers publish many formulas to estimate GFR from serum creatinine, but the most studied and widely used formulas in adults are Cock croft –Gault (C-G), Modification of Diet in Renal Disease (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) study equations (Baumgarten and Gehr, 2011).

Cock croft and Gault equation is one of the most widely used formulas to estimate creatinine clearance with consideration of age and weight, which is more accurate for older CKD patients (Snyder and Pendergraph, 2005), but CKD patients with extreme age (younger or very older), weight extreme (very low/high), malnutrition, skeletal muscle diseases, paraplegia, pregnancy, and vegetarian diet are exceptional that requires 24-hour urine collection for creatinine clearance (Snyder and Pendergraph, 2005). The C-G formula is;

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age in year}) \times \text{weight in kg}}{72 \times \text{serum creatinine}} \times 0.85 \text{ if female}$$

The Cockcroft and Gault formula is also very important measurement method for drug adjustment that excreted in the kidney like aminoglycoside (Lamb *et al.*, 2005).

Modification of Diet in Renal Disease (MDRD) study equation become more accurate for the estimation of GFR than Cockcroft and Gault formula from serum creatinine by taking age, sex, and race, which is good way of GFR estimation in CKD patients with middle age adults, comorbidities with CKD like diabetes and hypertension, and kidney transplant patients (Levey *et al.*, 1999). In MDRD, estimated glomerular filtration rate can be calculated as:

$$\text{GFR (mL per minute per 1.73 m}^2) = 186 \times (S_{cr} \text{ in mg/dL})^{-1.154} \times (\text{age in year})^{-0.203} \times (0.742, \text{ if female}) \times (1.210, \text{ if black}).$$

The Cockcroft-Gault and MDRD equation overestimates and under estimates GFR respectively, especially MDRD under estimates GFR when it is more than 60 mL per minute per $1.73m^2$ (Baumgarten and Gehr, 2011). CKD-EPI equation become gold standard way of GFR estimation with low limitation compared to the former two and KDIGO 2013 recommends to use CKD-EPI formula to estimate GFR for screening and diagnosis of CKD (Levin *et al.*, 2013). CKD-EPI equation takes age, sex, race and serum creatinine level with formula of (Levey *et al*., 2009);

GFR = 141 x min (Scr/k, 1) $^{\alpha}$ x max (Scr/k, 1)$^{-1.209}$x0.993^{Age}x 1.018 (if female) x 1.159 (if black), where Scr is serum creatinine, k is 0.7 for females and 0.9 for males, α is -0.329 for females and -0.411 for males, min indicates the minimum of Scr/k or1, and max indicates the maximum of Scr/k or 1.

The normal GFR varies by age, sex, weight, ingestion of cooked meat, malnutrition, race, and after use of some drugs. Advising the people not to take meat before 12 hour of measuring GFR and asking history of medication are good to avoid underestimation or over estimation of GFR (Baumgarten and Gehr, 2011). In this study we preferred the two most recently used equations (MDRD and CKD-EPI) to get estimated glomerular filtration rate. Measuring serum creatinine is the first step to get estimated GFR.

Creatinine is an amino acid derivative with a molecular mass of 113 Dalton and has no any physiological role, so removed from the body through urine after kidney filtration (Stevens *et al.*, 2006). It is an end product of phosphocreatine during muscular activity (Wyss and Kaddurah-Daouk, 2000). Phosphocreatine is highly energy rich phosphate compound that is used as source of energy for short period of time usually for 4 – 5 seconds during extraneous physical activity like sprinter (Chatterjea and Shinde, 2011). Creatine Phosphokinase is an enzyme responsible for the formation of ATP and creatine from phosphocreatine, which is the most rapid ATP yielding pathway in the body with small amount and can be depleted within a short time (Wyss and Kaddurah-Daouk, 2000). The body uses ATP to do work and creatine uses for the recycling of APD and phosphocreatine when there is high ATP than become degraded into creatinine, which is waste product and excreted in the body following kidney filtration (Clark and Cecil, 2015). Creatinine is filtered by the glomerulus and secreted by proximal tubular cells for excretion (Stevens and Levey, 2005). Removal of water from the creatine in the muscle results creatinine, which will transport to kidney through blood plasma for excretion (Chatterjea and Shinde, 2011).

Creatine can be obtained from the diet or can be synthesized in the liver and kidney from arginine, glycine, and methionine then transported to most creatine utilizing cells like muscle and brain cells through the blood stream by a specific protein transporter (Clark, 1997). Creatinine formation is a two-step process, transamidination of arginine and glycine (transfer of amidine group from arginine to Glycine) to form guanidoacetate (Glycocyamine) at kidney followed by methylation of Glycocyamine at liver to form active creatine (Brosnan *et al*., 2011). The methylation reaction needs magnesium and ATP (Wyss and Kaddurah-Daouk, 2000).

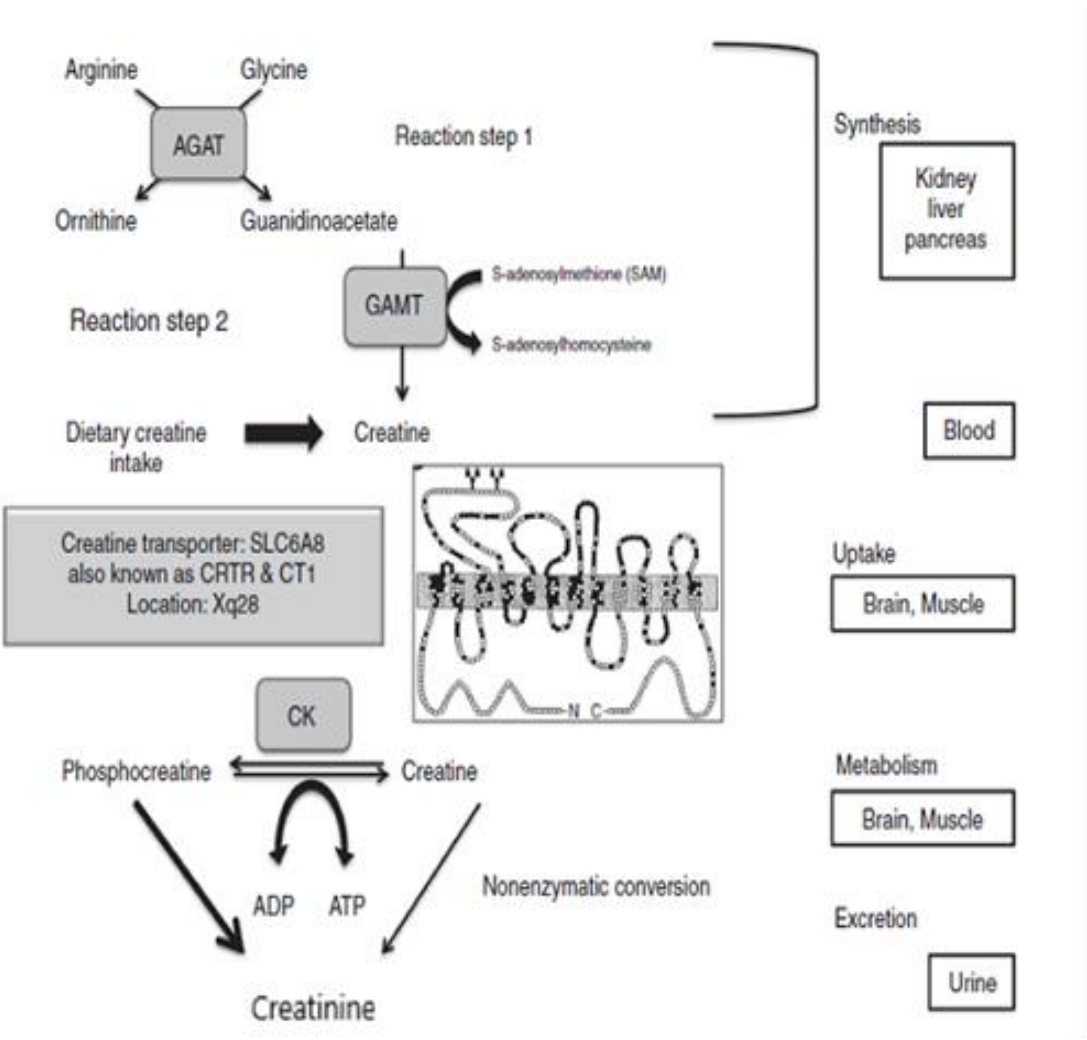


Figure 1 Schematic overview of creatine pathway

AGAT produces guanidinoacetate and ornithine from glycine and arginine. Guanidinoacetate is subsequently converted to creatine by GAMT then creatine phosphate is produced by creatine kinases. Around 2% of the total creatine content is non-enzymatically converted to creatinine per day, which is excreted through urine. Solute carrier family 6, member 8 (*SLC6A8*), also known as CRTR and CT1, represent the creatine transporter. ADP, adenosine diphosphate; AGAT, arginine glycine acyl transferase; ATP, adenosine triphosphate; CK, creatine kinase; GAMT, guanidinoacetic acid methyl transferase (Clark and Cecil, 2015).

Creatinine level can be measured by detecting serum creatinine level or by measuring creatinine clearance through 24 hour urine collection (Baumgarten and Gehr, 2011). Serum creatinine can vary among gender difference, geographical, and racial difference, which may be due to the difference in the dietary intake of creatine and difference in muscular mass (Jones *et al.*, 1998, Levin *et al.*, 2013). Under normal condition males have higher serum creatinine value than females because of their muscularity and the range of normal value depends on the laboratory set up (Wyss and Kaddurah-Daouk, 2000).

Proteinuria is another common laboratory finding for CKD and it is a good indicator of CKD progression, cardiovascular disease occurrence, and associated mortality risk (Fraser *et al*., 2014). Proteinuria can be defined as, abnormal excretion of small molecular mass proteins like albumin and immunoglobulin with urine. Urinary protein excretion can be measured as total protein or albumin (Atkins *et al.*, 2003). Albuminuria is the most widely used marker for kidney damage and the researchers are suggested to use urinary albumin to creatinine ratio in spot urine (Moyer, 2012, Levin *et al.*, 2013). Albumin is water soluble non glycosylated protein that grouped under globular protein with molecular mass of 65–70 kDa, which founds in the plasma in high amount and very important for the transportation of water insoluble compounds like short chain fatty acids (Chatterjea and Shinde, 2011). Urinary albumin/creatinine ratio in normal adults is less than 30 mg per g and above 30mg per g is an indication of kidney damage. The ratio between 30 to 300 mg per g is called micro albuminuria and more than 300 mg per g is called macro albuminuria (Gilmore, 2006). Micro albuminuria is an indicator of vascular permeability increment, which can be resulted due to diabetes, obesity and inflammation whereas macro albuminuria is a typical indicator of kidney damage (CKD) (Jones *et al.*, 2002).

1.1.2. Diagnosis and Staging of Chronic Kidney Disease

Most of the time CKD at early stage is asymptomatic or may be manifested some non-specific symptoms like feeling of unwell, loss of appetite, and hematuria. It became symptomatic at its severe form (end stage),which is difficult to treat and prevent the complications (Webster *et al.*, 2017), so early screening and diagnosis of CKD is fully based on the laboratory findings. Most researchers are advised to screen the populations at high risk of CKD (Snyder and Pendergraph, 2005, Baumgarten and Gehr, 2011).The first guidelines for the diagnosis, classification, and treatment of CKD were published in 2002 by US kidney disease outcome quality initiative group

(KDOQI) (Hogg *et al.*, 2003), which is used as a baseline for kidney disease improving global outcome (KDIGO) to adopt clinical practice guideline for the evaluation and management of CKD published in 2012 (Levin *et al*., 2013).

Current diagnosis and staging/classification of CKD is based on the KDIGO 2012 guideline by taking estimated GFR and albuminuria as a main investigation. The diagnosis involves persistent reduction of kidney function detected by eGFR and/or findings of kidney damage (Levin *et al.*, 2013). According to international guidelines (KDIGO 2012), CKD can be diagnosed; GFR <60 mL/min per 1·73m² and/ or at least one marker of kidney damage that persist for minimum of three months. Kidney damage markers are albuminuria (albumin: creatinine ratio [ACR] ≥30mg/g), urinary sediment abnormality, electrolyte abnormality, abnormalities on histology, structural abnormalities detected by imaging, history of kidney transplantation (Levin *et al.*, 2013). CKD staging is critical step to determine the prognosis, evaluation, and management of CKD irrespective of the risk factors and diagnosis (Baumgarten and Gehr, 2011), which can be classified into five stages see table 1.

Table 1 Classification of CKD adopted from KDIGO 2012 guideline, Addis Ababa, Ethiopia, 2018.

L low risk, M moderately increased risk, H high risk, and VH very high risk.

				Albuminuria description and range		
				A1	A2	A3
				<3mg/mmol Normal/mildly increase	3-30mg/ mmol Moderately increase	>30mg/mmol Severely increase
Estimated GFR (mL/min/1.73m^2 Range and description	G1	≥90	Normal/high	L	M	H
	G2	60-89	Mildly decrease	L	M	H
	G3a	45-59	Mildly to moderately decrease	M	H	VH
	G3b	30-44	Moderately to severely decrease	H	VH	VH
	G4	15-29	Severely decrease	VH	VH	VH
	G5	<15	Kidney failure	VH	VH	VH

1.1.3. Complication of CKD

Chronic Kidney Disease (CKD) patients with GFR less than 60 mL per minute per 1.73m^2 are at high risk for the development of complications, which can affect every organ and system so clinical and laboratorial follow up are very essential for the detection and early control of CKD complications (Thorp *et al.*, 2006). Over time CKD progresses into ESRD (requires kidney replacement), which facilitates the progression and mortality rate of comorbidities like cardiovascular disease (Levin *et al.*, 2013). The studies showed that over five year period, 1.1% of people with CKD stage two, 1.3% of people with CKD stage three, and 19.9% of people with CKD stage four requires dialysis or kidney transplantation (Keith *et al.*, 2004). Once CKD is diagnosed, systemic evaluation of clinical and laboratory finding is a key method for early detection of CKD complication.

Some of the Laboratory tests that show CKD complications are serum electrolyte abnormalities and normocytic, normochromic red blood cell (Snyder and Pendergraph, 2005). Clinical finding of gastrointestinal symptom like anorexia, vomiting, and abdominal discomfort are a sign of uraemia occurrence, which is systemic inflammatory disorder resulted from impairment of uric acid excretion and requires immediate dialysis or kidney transplantation (Gupta *et al.*, 2009). uraemia can also resulted due to infection or hemodialysis induced activation of the immune cell as well as leakage of endotoxin bacteria in to the circulation caused by CKD associated intestinal barrier dysfunction (Andersen *et al.*, 2016).

The common complications of CKD in adults are electrolyte derangement, anemia, metabolic acidosis, mineral bone disorder, arterial hypertension, hyperuricaemia and the progression of CVD (Romagnani *et al.*, 2017). Globally, the major causes of death in CKD is CVD accompanied with dyslipidemia, hyperuricaemia and hypertension (Thomas *et al.*, 2017). Complication may also asymptomatic until late stage and the international guidelines are suggested to detect complication following stage 3 (Cirillo *et al.*, 2006, Levin *et al.*, 2013). Other researcher also showed that ESRD patient on dialysis have higher chance to get cancer than those, who are kidney transplant patients but even high when compared with the general population, which is 10-80% and 1.9-9% respectively done on population based cohort study (Vajdic *et al.*, 2006, Holley, 2007).

Anemia is one of the common complication in CKD, which characterizes by normocytic, normochromic anemia (normal size of red blood cell and normal hemoglobin level respectively) is caused by multiple factors, but the most common cause of anemia in CKD is the reduction of erythropoietin production by kidney (Romagnani *et al.,* 2017). Erythropoietin (EPO) is a glycoprotein hormone used as signaling molecule to stimulate the production of RBC at bone marrow during low oxygen level in the cell and essential for the regulation of hemoglobin homoeostasis. It produces by interstitial fibroblasts around peritubular capillaries and proximal convoluted tubules, but during CKD the production become low and this results anemia (Webster *et al.,* 2017, Romagnani *et al.,* 2017).

Other factors of anemia in CKD patients are short lifespan of red blood cells, uraemia induced inhibitors of erythropoiesis, impaired intestinal iron absorption due to impairment of hepcidin (main regulator of iron) and blood losses during dialysis. Clinically, sign and symptom of anemia like easily fatigue, blurring of vision, pallor, low tolerance for exercise and other finding may occur (Romagnani *et al.,* 2017, Webster *et al.,* 2017). The occurrence of anemia in CKD patient facilitates the progression of CKD and associates with sleep disturbance, cognitive impairment and comorbidities like CVD, even can increase the mortality rate of the patients (van Nooten *et al.,* 2010).

Cardiovascular disease (CVD) is another common complication of CKD and being CKD patient increases risk of getting CVD by two to four times than the general population (Gansevoort *et al.,* 2013) and risk of mortality rate by cardiovascular disease complication increases by more than hundred times than the general population (Foley, 2010). The molecular mechanism of CVD development in CKD patient is not fully understood, but findings showed that vascular degeneration (resulting from endothelial dysfunction, arterial stiffness, and vascular calcification) caused by atherosclerosis process and inflammatory cytokines as well as ventricular hypertrophy with dilatation resulting from arterial hypertension, anemia and hypervolemia are the main risk factor for the development of CVD and its complication (Grabner *et al.,* 2015, Jimbo and Shimosawa, 2014). In addition both CKD and CVD share common risk factors such as smoking, obesity, hypertension, diabetes mellitus, and dyslipidemia, which may contribute to the occurrence of CVD along with CKD, but most of the time the clinician doesn't give attention for CVD in CKD patients and results higher adverse outcomes including disabling and death. Mineral bone disorder resulting from calcium and phosphorous metabolism disorder,

hyperparathyroidism, and dysregulation of vitamin D in CKD patient may also contribute the development of CVD with its complication (Said and Hernandez, 2014, Moe *et al.,* 2006)

Different researcher also showed that CKD, diabetes and CVD are interrelated each other. CKD and diabetes are risk factor for CVD and the reverse is also true. some of the metabolic pathway that interrelate CVD, diabetes, and CVD are hyperactivity of the renin angiotensin aldosterone system (RAAS), inflammation, osmotic sodium retention, endothelial dysfunction, dyslipidemia, and phosphatidylinositol 3- kinase (PI 3-kinase)-dependent signaling pathways (Gajjala *et al.*, 2015).

RAAS is one of the prominent molecular factors for the progression of CKD with comorbidities like CVD and diabetes. Renin produced by kidney is the initial step for RAAS in response of decreased renal perfusion, which activates angiotensinogen produced by liver into angiotensin-I and it is the rate limiting step than angiotensin converting enzyme produced by lung cells and lymphocytes will convert angiotensin-I into angiotensin-II (Gajjala *et al.,* 2015). Angiotensin II is an active peptide that mediate through G-protein coupled receptors such as angiotensin type 1 (AT1) and angiotensin type 2 (AT2) receptors, which expresses in many tissues or MAS receptor highly expressed in fetal and can also express in adrenal, ovary, brain, heart, and uterus of adults (Lavoie and Sigmund, 2003, Calò *et al.,* 2010). RAAS under pathophysiological (CVD, diabetes, and CVD) is summarized in figure 2.

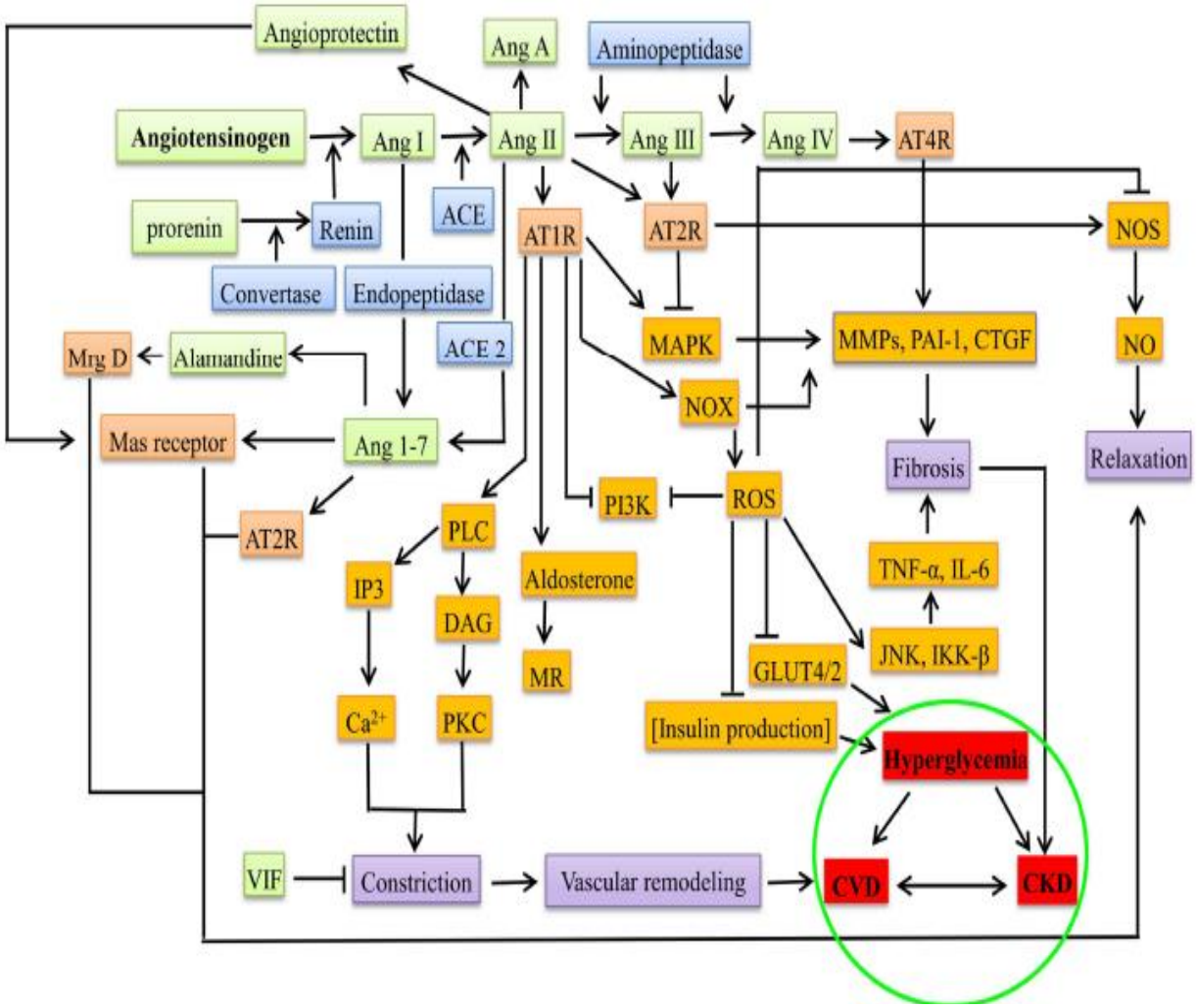


Figure 2 RAAS system under pathological conditions

*Ang, angiotensin; ACE, angiotensin converting enzyme; AT1R, angiotensin type 1 receptor; AT2R, angiotensin type 2 receptor; AT4R, angiotensin type 4 receptor; Mrg D, Mas-related G-protein coupled receptor membrane D; VIF, vasodilation inducing factor; PLC, phospholipase C; DAG, diacylglycerol; IP3, inositol triphosphate; PKC, protein kinase C; MR, mineralocorticoid receptor; PI3K, phosphoinositide 3-kinase; MAPK, mitogen-activated protein kinase; NOX, NADPH oxidase; ROS, reactive oxygen species; MMPs, matrix metalloproteinases; PAI-1, plasminogen activator inhibitor-1; CTGF, connective tissue growth factor; TNF-α, tumor necrosis factor alpha; JNK, c-Jun N-terminal kinases; IKK-β, inhibitor of nuclear factor-kappa-B kinase; NOS, nitric oxide synthase (Gajjala *et al*., 2015)

Metabolic acidosis is another common complication of CKD due to impairment of acid-base homeostasis ability by kidneys leading to accumulation of acids (Kovesdy, 2012). Each day 15,000 mmoL of carbon dioxide and 50 to 100 mEq of nonvolatile acid are produced in the body. Acid-base balance homeostasis is maintained by removal of carbon dioxide through lung and elimination of hydrogen as ammonia with bicarbonate reabsorption through kidney (Remer, 2000). Metabolisms of sulfur containing amino acids are the major source of acid in the body as sulfuric acid (Bailey, 2005). Reduction of functional nephrons in CKD causes the impairment of acid excretion as ammonia and results in abnormal elimination of bicarbonate with urine (Chen and Abramowitz, 2014). Initially acid-base homeostasis in CKD are maintained by increasing the excretion of ammonia but the retention of hydrogen becomes worse when GFR is less than 30mL/min at which the functional nephron dramatically reduces (Kovesdy, 2012).

High retention of acids in advanced CKD at which the plasma bicarbonate concentration is between 12–20 mEq/L will result in various adverse effects including progression of CKD, bone demineralization (uremic induced bone disorder), acidemia, and increasing of protein catabolism resulting in muscle wasting (Kalantar-Zadeh *et al.,* 2004; Kovesdy *et al.,* 2008). The treatment of metabolic acidosis in CKD is based on KDIGO 2013 guideline and recommends alkali therapy usually sodium bicarbonate or sodium citrate to sustain serum bicarbonate concentration in the standard range (23 to 29 mEq/L) (Sud *et al.,* 2014). CKD can also develop Hyperuricaemia (abnormal elevation of serum uric acid) resulting from the reduction of urinary uric acid elimination. Elevation of serum uric acid by itself can aggravate the progression of CKD as well it can accumulate in the joint that further results arthritis (Romagnani *et al.,* 2017). Other common disorders related to CKD are abnormal lipid metabolism leading to high triglyceride and low HDL, arterial hypertension and endocrine dysfunction (Romagnani *et al.,* 2017).

Complications associated with CKD are serious and fetal, but can be prevented or delayed by appropriate medication and modification of life style, so early screening and detection of CKD in the population is the crucial step to reduce the morbidity and mortality of CKD. Identification of risk groups and risk minimization is very essential to prevent CKD and its complication.

1.1.4. Electrolyte and their derangement in CKD

Electrolytes are essential minerals that found in the body fluid including blood and dissolves with water in order to create ions. The most nutritionally important electrolytes are sodium, potassium, magnesium, calcium, and phosphate. Those electrolytes can be found in the extracellular fluid or in the intracellular fluid in regulated manner (Marzoq *et al.,* 2016). Electrolytes are involved in different physiological roles in the body such as acid- base regulation, maintenance of fluid balance, act as cofactor for different enzymes, involve in nerve impulse, promote muscle contraction, and involve in the mineralization of bone (Liamis *et al.*, 2013).

Serum electrolyte disturbance is multifactorial that can result due to hypertension (Bell *et al.*, 2015), diabetes mellitus (Liamis *et al.,* 2014), myocardial infarction (Takano *et al.,* 2018), thyroid disorder (McCance and Huether, 2015), acute infection (Fowler *et al.,* 2014), CKD (Langston, 2017) and other chronic non communicable diseases. In addition to this, electrolyte derangement can be resulted due to nutritional status, defect in absorption, acid-base dysregulation, and pharmacological drugs (Liamis *et al*., 2014). The progression of CKD is one of the commonest cause of electrolyte disorder especially in those who are near to ESRD, this will increase the mortality rate because kidney is the organ that play a key role in electrolyte regulation (Dhondup and Qian, 2017). The commonest electrolyte disorders associated with renal failure are potassium, sodium, magnesium, phosphorus, and calcium derangement that can further lead to serious complications like bone demineralization, muscle wasting, vascular calcification and even can result in death (Dhondup and Qian, 2017).

1.1.4.1. Sodium disorder in CKD

Sodium is the most extracellular cation that maintains internal fluids along with potassium (major intracellular cation) through sodium-potassium pump, which is also important for muscle and nerve cell impulse conduction (Pohl *et al*., 2013). Sodium-potassium pump also called Na^+-K^+-ATPase is a glycoprotein made up of two (α and β) chains. The presence of Na^+ and K^+ determines the activity of it with the involvement of ATP and Mg^{++} as cofactor (Chatterjea and Shinde, 2011). Sodium absorbs in the intestine and excretes mainly through urine and can also through faces, sweat, and tears. Usually the dietary intake is in the form of salt and high salt intake is risk factor for chronic non-communicable diseases including renal failure (Trieu *et al*.,

2015). Due to this reason world health organization (WHO) recommends daily salt intake must be less than 5gm, but globally most peoples take more than it and believed to be one of the reasons for the rapid increase of NCDs in the world (WHO, 2012). Sodium levels in the body can be regulated through the stimulation of thirsty to drink more water and stimulation of antidiuretic hormone (ADH) secretion to reabsorb water in the kidney tubule after glomerular filtration during high sodium level and the reverse is true during low sodium level (Pohl *et al*., 2013).

Kidney is the main organ that dilute or concentrate urine (water homeostasis), but as CKD progresses, the ability of glomerular filtration become impaired and then lead to dysnatremias (Schrier *et al*., 2013). Dysnatremia is a condition that shows abnormal body water homeostasis that may be high or low in the body. It can be interpreted by the level of sodium as hypernatremia (serum sodium >145mmol/L) and as hyponatremia (serum sodium<135 mmol/L), to indicate deficient and excess water compared to sodium level in the body respectively (Dhondup and Qian, 2017). Globally, hyponatremia is the most common electrolyte disorder in hospitalized patients as well as in the community that facilitate the progression of the disease and mortality rate (Olsson *et al.*, 2013). In CKD the prevalence and incidence of dysnatremia is not well studied, but believed to be higher compared to the general population because CKD progression can result the impairment in the diluting or concentrating mechanisms of urine (Combs and Berl, 2014). Different researcher support this idea and states that hyponatremia is one of the main independent risk factors to increase the mortality rate in CKD patients on dialysis and can also raise the risk of getting ESRD as well as increases the mortality rate of non-dialysis CKD patients (Han *et al*., 2015, Chiu *et al*., 2016). In CKD patients hyponatremia is more common than hypernatremia because the kidney is incapable to reabsorb sodium leading to abnormal excretion via urine and results low sodium level compared to water in the body (Chatterjea and Shinde, 2011)

1.1.4.2. Potassium disorder in CKD

Potassium is the foremost intracellular cation, which is very important for protein synthesis from amino acids, glycogen synthesis from glucose, act as cofactor for some enzymes like pyruvate kinase, involve in nerve impulse conduction, involve in acid-base homeostasis, involve in muscular contraction, and in the maintenance of normal cardiac rhythm (Chatterjea and Shinde,

2011). Under normal physiological condition, plasma potassium concentration is between 3.5-5 mEq/L and the majority (98%) of potassium founds intracellular, which regulates by sodium-potassium pump and renal potassium homeostasis (Boyd-Shiwarski and Subramanya, 2017). Around 90% of dietary Potassium is absorbed in the intestine with frequent entry into portal circulation, and the remaining excretes through faces. Serum potassium level can be maintained by insulin, catecholamine, PH, and renal homeostasis (Boyd-Shiwarski and Subramanya, 2017). Each day urinary excretion of potassium is run approximately in constant range through glomerular filtration followed by proximal tubule and loop of Henle reabsorption/secretion (Pohl *et al*., 2013).

During CKD the regulation of potassium became disrupted due to the reduction of functional nephrons, which is the main risk factor for cardiovascular disease occurrence and death (Luo *et al.*, 2016). In CKD patients one of the common electrolyte disorders is hyperkalemia resulting from decreased glomerular filtration and tubular K+ secretion. This problem is worse when CKD progresses in to ESRD with poor outcome (Einhorn *et al*., 2009). Hyperkalemia is defined as abnormal elevation of serum potassium level above the normal value (>5.0 mEq/L) (Chatterjea and Shinde, 2011). Other causes of hyperkalemia in CKD are metabolic acidosis resulting potassium shift into extracellular space and reduction of renal potassium excretion due to medications such as ACEI, ARB, non-steroidal anti-inflammatory drugs, potassium supplement, and potassium sparing diuretics (Dhondup and Qian, 2017).

1.1.4.3. Magnesium disorder in CKD

Magnesium is the fourth most abundant electrolyte next to sodium, potassium, and calcium and second most intracellular cation next to potassium in the body, which contributes for more than 300 enzymatic reactions as cofactor (Gröber *et al*., 2015). Most ATP dependent biochemical reaction needs Mg^{2+} as cofactor. As it involves in many biochemical and physiological role in the body humans must take magnesium daily, unless deficiency can result in various inflammatory and chronic metabolic diseases like type 2 diabetes mellitus, cardiovascular disease, Alzheimer's disease, asthma, hypertension, insulin resistance, and osteoporosis (Song *et al.*, 2005).

More than 99% of total body magnesium founds in bone, muscles and non-muscular soft tissue and the major reservoir is bone and in the extracellular fluid only1–2% of total body magnesium

founds, so measuring serum magnesium level may not show total body stores (Spiegel, 2011). like that of other electrolytes, magnesium excretion is regulated by kidney through glomeruli filtration followed by tubular reabsorption and/or secretion, but progression of CKD results the defect of this process and results dysmagnesemia (Jahnen-Dechent and Ketteler, 2012). Other factors that affect tubular reabsorption are Plasma magnesium status, hormones like PTH and calcitonin, phosphate depletion, and acid base states of the body (Ağaoğlu *et al*., 2011). Dysmagnesemia (abnormal high or low level of serum magnesium) is common electrolyte disorder in CKD patients during advanced reduction of estimated glomerular filtration rate (Cheungpasitporn *et al*., 2015). Hypomagnesaemia is more common problem than hypermagnesaemia in CKD patients due to poor regulation of magnesium by kidney and results excess excretion through urine (Floege, 2015)

1.1.4.4. Calcium and Phosphorus disorders in CKD

Calcium and phosphorus are the two most electrolytes located in the bone (99% and 85%) respectively and the rest located in the soft tissues and extracellular fluid (Chatterjea and Shinde, 2011). The regulation of those electrolyte follows the same manner and the main regulatory systems involve gastrointestinal absorption, bone resorption, and kidney excretion (Blaine *et al*., 2014). Under normal condition the net dietary intake of calcium and phosphorus is equivalent to excretion through kidney by physiological adjustment. Increasing or decreasing of gastrointestinal absorption, bone resorption, and renal tubular reabsorption maintains plasma calcium and phosphorus level (If low calcium, increases and if high calcium, decrease) (Blaine *et al*., 2014). Actually calcium and phosphorus homeostasis is very complex process that can affect by hormones (Parathyroid hormone (PTH), glucocorticoids, and calcitonin), vitamin D metabolites, and dietary intake of them (Chatterjea and Shinde, 2011).

PTH regulates calcium and phosphorus by increasing bone mineralization, activation of 1α-hydroxylase, decreasing of phosphate reabsorption and increasing of calcium reabsorption in kidney (Bhagavan, 2002). 1 α –hydroxylase is an enzyme that found in kidney, which is responsible for the synthesis of active vitamin D metabolite called 1,25-dihydroxyvitamin D3 (calcitriol) from 25-hydroxyvitamin D (calcidiol) than calcitriol stimulates/ increases intestinal and/or renal absorption and bone resorption of calcium and phosphate during stores in the body (Bhagavan, 2002). PTH regulates by negative feedback mechanism by ionized plasma calcium

concentration and calcitriol. It also regulates by magnesium, hypermagnesaemia inhibits the secretion of PTH (Chatterjea and Shinde, 2011).

Kidney regulates calcium and phosphate by glomerular filtration followed by tubular reabsorption and/ secretion, excess will be excrete through urine. Proximal tubule is the major site of reabsorption without the influence of hormones, but reabsorption by distal tubule is PTH dependent during low store (Chatterjea and Shinde, 2011). Chronic kidney disease is one of the main factors that disrepute this regulatory-path way due to reduction of functional nephron and results the impairment of filtration as well as reabsorption of calcium and phosphate. Dysregulation of calcium and phosphate in kidney failure further results bone turnover abnormality and soft tissue and vascular calcification called CKD related mineral bone disorder (CKD-MBD) (Moe *et al*., 2006).

Chronic kidney disease related mineral bone disorder (CKD–MBD) is a condition characterized by defect of bone remodeling (cellular process that balance bone formation and resorption) accompanying with loss of bone mass and abnormal bone structure, which is one of the main risk factor for fracture and death of the patient (Zheng *et al*., 2016). Varies researcher shows high risk of getting hip fracture among advanced CKD patients on dialysis and the prevalence is high compared to the general population regardless of age and sex (Danese *et al*., 2006, Alem *et al*., 2000, Tentori *et al*., 2014). They also report that dialysis increases the mortality rate of patients with hip fracture especially in older age and long duration of dialysis (Alem *et al*., 2000, Danese *et al*., 2006).

The clinical and laboratorial finding of CKD-MBD can be any combination of the following: high serum phosphate and PTH, low/normal/high serum calcium concentration resulting from abnormal metabolism of calcium, phosphate, vitamin D, and PTH, bone pain, bone fragility, and soft tissue calcification including blood vessels due to abnormality of bone turnover and mineralization (Webster *et al*., 2017). As CKD progresses, deficiency of calcitriol (active form of vitamin D) will result due to 1 α – hydroxylase secretion impairment by kidney, which will lead to hypocalcemia and secondary hyperparathyroidism leading to stimulation of bone osteoclast activity that further results reduction of bone density and increases bone fracture (Webster *et al*., 2017). Restriction of dietary phosphate, provision of calcium or active vitamin D is the treatment of chose for progressive CKD with mineral bone disorder (Levin *et al*., 2013).

1.1.5. Treatment of CKD

The decision to start treatment is the critical point for CKD to prevent the progression of CKD and its adverse effect. Before treatment starting, CKD staging, identification of the comorbid conditions, evaluation of presence/absence of complications, and evaluation of loss of kidney function risks must be considered to give effective treatment (Levey *et al*., 2003). The treatment option of CKD can be dietary modification, life style modification, symptomatic treatment like proteinuria, treatment of the underline cause, treatment of the specific complications, dialysis, and finally kidney transplantation, which is considered as gold standard therapy for CKD patients especially at ESRD (Levin *et al*., 2013).

To see the improvement of CKD, monitoring GFR and proteinuria are the most important therapeutic approach to prevent or delay the complication of CKD. In middle and low income countries including Ethiopia the mortality rate of CKD patients are high because of lack of early screening or diagnosis, shortage of facilities like kidney replacement center, cost of dialysis, and poor life style of the patients (Stanifer *et al*., 2014). ESRD can be treated with dialysis or kidney transplantation. The latter is best way of treatment to increase the survival rate of the client and to minimize the side effect of dialysis. The treatment can be transformed from dialysis to transplantation because of this benefit and usually the physicians are advised to choose kidney transplantation over dialysis for ESKD and for those who are on dialysis (Goldfarb-Rumyantzev *et al*., 2005, Helal *et al*., 2015). The therapeutics approach of CKD is summarized in table 2

Table 2 Therapeutic approach for CKD, Addis Ababa, Ethiopia, 2018.

Therapy	Comment	Reference
Dietary modification (Restrict sodium and high protein diet with dose adjustment in each stage), eat fruits, vegetables, fish, and low fat and carbohydrate diets	To reduce CKD progression and to control hypertension	(Rughooputh *et al*., 2015, Robertson *et al*., 2007, Fouque and Laville, 2009, Jones-Burton *et al*., 2006, McMahon *et al*., 2015, Sabatino *et al*., 2017)
Lifestyle modification (exercise, no smoking, no drinking, reduce weight and psychological treatment and education)	to reduce risk of cardiovascular disease	(Esser *et al*., 2014, Nakamura *et al*., 2015, Matsumoto *et al*., 2017)
ACEI and/or ARB in hypertensive CKD patients	To reduce CKD progression and to reduce risk of cardiovascular disease (by reducing proteinuria), and to control hypertension	(Strippoli *et al*., 2005, Wang *et al*., 2017, MacKinnon *et al*., 2006, Mavridis *et al*., 2016)
non-dihydropyridine calcium channel blockers	To reduce CKD progression and proteinuria, who are intolerant of ACEI or ARB	(Bakris *et al*., 2004, Tabur *et al*., 2015)
antiplatelet therapy (aspirin)	To reduce/prevent CVD risks	(Trialists'Collaboration, 2002, Udell *et al*., 2015, Wood, 2006)
Erythropoiesis stimulating agents	To treat anemia	(Tamura *et al*., 2016, Drüeke *et al*., 2006, Locatelli *et al*., 2008)
Alkali therapy (Sodium bicarbonate)	To treat metabolic acidosis	(Goraya and Wesson, 2017, Wesson, 2016, Mathur *et al*., 2006)
Treatment of underlined causes or comorbidities like diabetes, HIV, and CVD accordingly	To delay or prevent the progression and mortality of CKD	(Stanifer *et al*., 2014, Inker *et al*., 2014, Akbari *et al*., 2015)
Hemodialysis (HD) or peritoneal dialysis (PD)	To filter waste products from the body and to eliminate /remove extra fluid from the blood at ESRF and for pre-transplant preparation	(Helal *et al*., 2015, Habbous *et al*., 2018)
Kidney transplantation	Treatment of irreversible kidney failure	(Sibulesky *et al*., 2017, Liyanage *et al*., 2015, Levin *et al*., 2013)
Active vitamin D	To treat CKD-MBD in stage3 and 4 CKD	(Levin *et al*., 2013)

1.1.6. Epidemiology

Globally, the prevalence and incidence of CKD varies due to different reasons such as estimation of GFR by using different formula, use of different methods to measure proteinuria, lack of symptoms until end stage renal failure, and lack of population based study on CKD especially in low and middle income countries (Webster *et al.*, 2017). According to 2016 meta-analysis, the global prevalence of CKD is estimated between 11 to 13% with the majority of stage 3 and the prevalence of all stages in different country is estimated between 7–12% , which is very high (Hill *et al.*, 2016). The prevalence of CKD in high income countries are reported to be around 11% (Webster *et al.*, 2017). According to global burden of disease 2012 report globally, CKD is 18thhighest cause of death with rapid increasing rate between1990 and 2010 with high burden in low and middle income countries including sub Saharan countries (Lozano *et al.*, 2012).

According to 2016 meta-analysis report, the foremost (80%) of CKD patients are live in low and middle income countries, which is estimated between 14.3% and 36.1% of prevalence with more than 500000 patient incidence rate of ESRD annually, resulting in premature death in most cases (Stanifer *et al.*, 2016, Ene-Iordache *et al.*, 2016). By 2030 the majority (70%) of ESRD is estimated to be found in the developing countries (Naicker, 2010). The average prevalence of CKD in Africa is 10.1% with highest proportion (16.5%) found in West/Central West Africa (Elhafeez *et al.*, 2018). According to 2014 report, the prevalence of CKD in Sub Saharan Africa countries is estimated to be 13.9% and for the next decade kidney disease will increase rapidly due to urbanization, epidemic of HIV, and increasing rates of non-communicable diseases, which are the risk factors for CKD (Stanifer *et al.,* 2014). The worst aspect of CKD in sub-Saharan countries is, it affects mostly young productive adults and mortality rate is very high due to lack of early screening and treatment facility (Arogundade and Barsoum, 2008).

In Ethiopia, there is no published report on the incidence, prevalence, and life expectancy of CKD patients, but believed to be high because of lack of early screening, inability of cost affordability for dialysis, and shortage of facility center, since there is only one renal transplantation center. Apart to this, a study conducted by Fiseha *et al* in 2014 at southern Ethiopia on the prevalence of CKD and associated factor among diabetes patient showed that, 23.8% and 18.2 % had CKD based on C-G and MDRD equations respectively (Fiseha *et al.*, 2014). The prevalence of CKD in Addis Ababa (capital city of Ethiopia) population is not well known.

1.1.7. Significance of the study

Recently Ethiopia faces a double burden problem because of rapid increase of NCDs including kidney disease due to different factors such as sedentary life style, aging, urbanization, increasing prevalence of obesity, smoking, drinking, and physical inactivity. CKD became one of the major silent killers in Ethiopia with increasing incidence rate because of rapid rise of hypertension and diabetes prevalence. The major problem of CKD in sub Saharan Africa country including Ethiopia is that it attacks most productive young adults and results in death. In Ethiopia early screening, detection, and identification of kidney disease risk groups are very rear and currently, sudden hearing of kidney failure and death due to CKD and its complication become common. In developing countries like Ethiopia treating the patient with ESRD and its complication is very difficult due to varies reasons such as lack of facility and even it is unaffordable. Therefore screening of CKD for early detection and evaluation is very important to minimize the burden of the community from it. However there are limited number of studies in Ethiopia and in the study area and the aim of this study was to assessed and screened the kidney function status by measuring the level of some electrolyte in the serum (serum sodium, chloride, potassium, magnesium, calcium, and phosphate level) and renal function tests (serum creatinine to evaluate the level of GFR) and the associated risk factors for CKD among the volunteers of Ethiopian Public Health Institute Staff Members. As far as our knowledge is concerned there is limited study on CKD in Ethiopia as well as the study area and we believe it will be a big input for health professionals and policy makers for prevention and risk minimization of end stage renal failure.

1.1.8. Hypothesis

Chronic kidney disease (CKD) can be early detected without any clinical manifestation by measuring serum electrolytes and kidney function tests in the general population.

2. OBJECTIVE

2.1. General objective

- The objective of this study was assessing serum electrolyte levels and kidney function tests for screening and early detection of CKD and to detect the associated risk factors among Ethiopian Public Health Institute (EPHI) Staff Members, Addis Ababa, Ethiopia.

2.2. Specific objectives

- To determine the level of serum electrolytes in Ethiopian Public Health Institute Staff Members.
- To assess kidney function tests in Ethiopian Public Health Institute Staff Members.
- To detect the prevalence of chronic kidney disease in Ethiopian Public Health Institute Staff Members.
- To detect the associated risk factors for chronic kidney disease in Ethiopian Public Health Institute Staff Members.

3. MATERIALS AND METHODS

3.1. Study area and population

The study was conducted in Ethiopian Public Health Institute located in Addis Ababa, capital city of Ethiopia among staff members. Source population of the study were staff members of Ethiopian Public Health Institute and the study population were all volunteer staff members.

Table 3 Describing total staff members of EPHI by gender and academic background, Addis Ababa, Ethiopia, 2018

Job tittle	Female	Male	Total
Researcher	76	234	310
Admin staff	178	197	375
Technical staff	35	32	67
Contract staff	14	50	64
Over all total	303	513	816

3.2. Study design and period

Cross sectional study was conducted using WHO stepwise survey from January 2018 to October 2018

3.3. Inclusion and Exclusion criteria

Inclusion criteria

- Staff members of Ethiopian Public Health Institute from 18-69 years

Exclusion criteria

- Staff members of pregnant women
- Staff members suffered from acute infection including diarrheal disease
- Critically sick staff members

3.4. Sample size determination

To determine the sample size, we have used a two-step procedure. The first one was determining the sample size without considering the finite population correction factor and the second one

was determining the total sample size required using the finite population correction formula (Daniel.,1999). The prevalence of CKD in Ethiopian population was not well known, so we have used expected prevalence or proportion (P) 0.5 which undertakes maximum sample size with confidence interval 95% and margin of error 4%.

Step one; $n_0 = \frac{Z^2P*(1-P)}{d^2}$

Where n_0 = sample size without considering the finite population correction factor

Z = Z statistic for a level of confidence

P = expected prevalence or proportion

d = margin of error/precision

$n_0 = \frac{1.96^2 0.5*(1-0.5)}{(0.04)^2} = 600$

Step two; calculating the total sample size required using the finite population correction formula. $n = \frac{n_0*N}{n_0+ (N-1)}$

Where n_0 = sample size without considering the finite population correction factor

Z = Z statistic for a level of confidence

N = total population size

n = sample size required using the finite population correction factor

The total staff members of Ethiopian Public Health Institute were 816.

$n = \frac{600*816}{600+ (816-1)} = 346$

By considering 10% of non-response rate, the minimum sample size was 381 and these participants were selected based on voluntarism.

3.5. Variables in the study

Dependent variable

Serum electrolytes and kidney function tests

Independent variables

Socio demographic and Behavioral - Age, Sex, marital status, educational level, income per month, Alcohol consumption, Cigarette smoking, Herbal medication, Chat chewing

Clinical variables- systolic blood pressure, diastolic blood pressure, BMI, Hypertension, diabetes, cardiovascular disease, family history of renal disease, kidney stone, repeated UTI and/ or glomerulonephritis

3.6. Data Collection

Data collection procedure was successfully determined by the project data collection team. The team was organized by EPHI with St. Paul's Hospital collaboration. Professional nurses, laboratory technologists, and physicians were involved in the team to collect data including blood samples. The data collection procedure was under supervision by the principal investigator. The data collection team was trained by Senior researchers before data collection to address the objectives of the study. The training session were covered every detail of the study and the full range of skills involved in the study. The data contains questionnaire, anthropometric, and biochemical measurements. Electronic data collection method was implemented. The questionnaires, anthropometric, and biochemical measurements were uploaded into tablet computer and data was collected electronically. Then, the data was transferred through internet file streaming system (IFSS) to central server located at IT unit of EPHI. The data was secured and accessed by the principal investigators.

3.7. Questionnaire

A questionnaire was specifically developed per sample size, which helps to either including or excluding from the study. The questionnaire included the question that assessed the socio demographic characteristic such as Age, Sex, educational level, income per month, self/family history of renal disease, and comorbidities. WHO identified risk factors of NCDs with expanded and optional questions to suit local needs were also included in the questionnaire.

3.8. Anthropometric measurement

Physical measurements such as weight, height, and blood pressure were taken using standardized methods and adjusted equipment. Weight was measured in kilogram with light cloths and no wearing of shoes, the participants height was measured in centimeter using height board with no shoes wearing and in upright position then BMI was calculated to determine the obesity status (WHO, 2000). Blood pressure was measured according to WHO guideline using an automated sphygmomanometer at the midpoint of the lift arm after participants rest for at least five minutes or 30 minutes for those who take hot drinks like coffee. Three blood pressure readings were taken for all participants than the mean blood pressure was taken as true value (Chalmers, 1999).

3.9. Blood sample collection and processing

Five milliliter (5mL) of blood sample was collected early morning before breakfast or minimum of eight hour fasting into standardize serum separator tube from each participant by trained laboratory technologist. The process of blood sample collection was through aseptic/sterile technique. The blood sample was stored under ice bag immediately following blood drawing until transferred to National References Laboratory for Clinical Chemistry, Ethiopian Public Health Institute (EPHI) for analysis or stored at 2-8^{o}C until analysis was done. Serum was obtained from collected blood sample by centrifugation at 3000 rpm for 7minutes using Rotanta 960 centrifuge in thermo stable condition.

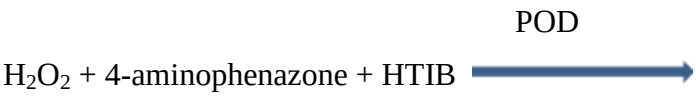
3.10. Biochemical analysis

1. Serum creatinine: - It is one of the major kidney function test and important for the estimation of GFR, which is recognized as the diagnosis tool for CKD regardless of the underline cause (Levin *et al.*, 2013). Serum creatinine was assessed by COBAS 6000 analyzer through the principle of enzymatic colorimetric method.

Enzymatic colorimetric method test principle

The method was based on the production of glycine, formaldehyde and hydrogen peroxide from creatinine that is catalyzed by creatininase, creatinase, and sarcosine oxidase (SOD). Finally quinone imine chromogen will produce with the aid of peroxidase (POD) that catalyzes the reaction of the liberated hydrogen peroxide with 4-aminophenazone and HTIBa. Creatinine

concentration in the reaction is directly proportional to the color intensity of the quinone imine chromogen formed (Roche Diagnostics Corporation, 2014).



The measuring mode of the test was absorbance, which calculated the analytes absorbance at end point with wavelength A/B of 552/659nm. COBAS 6000 analyzers automatically calculate the analyte concentration of each sample.

Expected normal values of serum creatinine in adults are; 45-84 µmol/L (0.51-0.95 mg/dL) for females and 59-104 µmol/L (0.67-1.17 mg/dL) for males (Dries *et al.*, 2000). Once we get serum creatinine level, we calculated eGFR using MDRD and CKD-EPI equation (Levey *et al.*, 1999, Levey *et al.*, 2009). In CKD the expected value were increased serum creatinine and decreased eGFR.

2. Urea/BUN: Urea is the end product of urea cycle from ammonia and must be excreted through renal perfusion. BUN along with creatinine is the two mostly requested tests to detect the kidney function (Whelton *et al.*, 1994). Serum urea/BUN was determined by COBAS 6000 analyzer.

Test principle

It is a kinetic test with the use of urease and glutamate dehydrogenase.

Ammonium and carbonate is produced from urea by urease followed by reaction of ammonium with 2-oxoglutarate to form L-glutamate by glutamate dehydrogenase (GLDH) and the coenzyme NADH (Roche Diagnostics Corporation, 2015).

$$\text{Urea} + 2\,H_2O \xrightarrow{\text{Urease}} 2\,NH_4^+ + CO_3^{2-}$$

$$NH_4^+ + \text{2-oxoglutarate} + \text{NADH} \xrightarrow{\text{GLDH}} \text{L-glutamate} + NAD^+ + H_2O$$

The rate of decrease in the NADH concentration measured photometrically at 700/340 nm is directly proportional to the urea concentration. Roche/Hitachi COBAS C systems automatically calculate the analyte concentration of each sample (Roche Diagnostics Corporation, 2015).

Expected normal values of serum urea and BUN for adults is 2.76-8.07 mmol/L (16.6-48.5 mg/dL) and 2.14-7.14 mmol/L (6-20 mg/dL) respectively (Löhr *et al*., 2009). During CKD both level became increased.

3. Serum sodium, potassium, and chloride

The level of serum sodium, potassium, and chloride were determined by ion selective electrode module of COBAS 6000 system.

Test principle

The method was based on the formation of electrical potential (electromotive force) on a certain membrane materials by ion-selective electrode (ISE) to measure the ions in solution. The solutions are test solution and internal filling solution. The electrode has a selective membrane in contact with both solutions. The internal filling solution contains the test ion at a fixed concentration. The test ion was closely associate with the membrane on each side due to the particular nature of the membrane. The membrane electromotive force (EMF) was determined by the difference in concentration of the test ion in the test solution and the internal filling solution. The EMF develops according to the Nernst equation for a specific ion in solution (Roche Diagnostics Corporation, 2015).

$E = E_O + RT/nF. \ln (f. c_t)/ (f. c_i)$

Where: E= electrode EMF, E_O = standard EMF, R = constant, T =temperature, n = charge of the ion, F = faraday's constant, In = natural logarithm, f = activity coefficient, c_t = ion concentration in test solution, c_i = ion concentration in internal filling solution

Expected normal values in adults

Serum sodium, potassium, and chloride are 135 – 145 mmol/L, 3.5 – 5.1 mmol/L, and 98-107 mmol/L respectively (Burtis and Bruns., 2014). In CKD patients hyponatremia (<135mmol/L and hyperkalemia (>5.1mmol/L) are the common finding.

4. Serum calcium: the level of serum calcium was determined on COBAS 6000 analyzer

Test principle

The method was based on calcium-NM-BAPTA complex formation through the reaction of Calcium ions with 5-nitro-5-methyl-BAPTA (NM-BAPTA) under alkaline pH (around pH of 10) then the complex reacts with EDTA (Roche Diagnostics Corporation., 2014).

$$Ca^{2+} + \text{NM-BAPTA} \xrightarrow{\text{Alkaline pH}} \text{calcium-NM-BAPTA complex}$$

$$\text{Calcium-NM-BAPTA complex} + \text{EDTA} \longrightarrow \text{NM-BAPTA} + \text{calcium EDTA complex}$$

The change in absorbance, which is directly proportional to the calcium concentration is measured photometrically at 340 nm (Bourguignon *et al*., 2014). COBAS 6000 analyzers automatically calculate the analyte concentration of each sample.

Expected normal values in adults (18-60 years); Serum calcium is 2.15-2.50 mmol/L (8.6-10.0 mg/dL) (Wu., 2006). The expected value of serum calcium in CKD patients is hypocalcemia (below 2.15mmol/L).

5. Serum phosphate: serum phosphate level was determined on COBAS 6000 analyzer

Test principle

Endpoint method with sample blanking

Inorganic phosphate reacts with ammonium molybdate in the presence of sulfuric acid to form ammonium phosphomolybdate complex having the formula $(NH_4)_3[PO4\ (MoO_3)_{12}]$. The complex was determined photometrically in the ultraviolet region at 340 nm wavelength. Accelerator can be added to get rapid reaction rate and more precise result will be gotten by application of sample blanking. COBAS 6000 analyzers automatically calculate the analyte concentration of each sample (Roche Diagnostics Corporation., 2016).

Expected normal values in adult

Serum phosphate is 0.18-1.45mmol/L (2.5-4.5mg/dL) (Burtis *et al*., 2012). The common finding in renal failure is hyperphosphatemia (>1.45 mmol/L).

6. Serum magnesium: the level of serum magnesium was determined on COBAS 6000 analyzer system.

Test principle

Colorimetric endpoint method

This method is based on the reaction of magnesium with xylidyl blue in alkaline solution containing EGTA. Magnesium forms a purple complex with xylidyl blue, diazonium salt. EGTA uses to mask the calcium in the sample. The magnesium concentration is measured photometrically at wavelength (sub/main) of 505/600nm via the decrease in the xylidyl blue absorbance. COBAS 6000 analyzers automatically calculate the analyte concentration of each sample (Roche Diagnostics Corporation, 2015).

Expected normal values in adult Serum magnesium is 0.66-1.07 mmol/L (1.6-2.6 mg/dL) (Wu, 2006)

3.11. Data quality assurance

For each phase of the study design, data quality control techniques were applied. The questionnaire were prepared by English version and translated into local language (Amharic). The data collectors were professional nurses, laboratory technologists, and physicians under the supervision of investigators and were trained before data collection was conducted to address the objectives of the study. Blood sample collection was done through standardized, calibrated, and sterile technique by professional laboratory technologists. Questionnaire pretest was taken before two weeks of concrete data collection to check the reliability of the data and to increase the quality of the data.

3.12. Data processing and analysis

From internet file streaming system (IFSS) of EPHI information technology unit, data was enter into Microsoft excel then cleaned and transferred into statistical package for the social science (SPSS) version 20 software for statistical data analysis. Descriptive data analysis were conducted and presented as frequency and percentage. Normal distribution of data were checked by Shapiro-wilk normality test, histogram, kurtosis, normal Q-Q plot, and box plot tests. Independent T-test were used to compare quantitative data's as mean and standard deviation. The data output was interpreted using tables and/or charts. We were also used chi-square test and binary logistic regression analysis to determine the association of risk factors with reduced glomerular filtration rate. P value < 0.05 was used as a statistical significance.

3.13. Ethical consideration

To conduct the research, ethical approval were obtained from Ethiopian Public Health Institute, Institutional Review Board (EPHI- IRB) with protocol number EPHI-IRB-082-2018 and Addis Ababa University Biochemistry Department Ethics and Research Committee (DRERC) with protocol number M.Sc. 09/18, meeting number DRERC 08/18. Informed consent was obtained from the participants before running the questionnaire and sample collection. All the principles of ethics such as informed consent, confidentiality, and privacy were kept. Data collection was without personal identifier or using codes. All study participants were read and sign on the informed consent. If the study participants were illiterate, the data collector was read and was taken the sign or thump impression when they become agreed.

3.14. Operational definition

Chronic Kidney disease was defined as eGFR< 60 mL/min/1.73 m^2 by both MDRD and CKD-EPI with or without electrolyte derangement.

End stage renal failure was defined as eGFR< 15 mL/min/1.73 m^2 by both MDRD and CKD-EPI with or without electrolyte derangement

Stage two kidney disease was defined as eGFR between 60-89 mL/min/1.73 m^2 by both MDRD and CKD-EPI with or without electrolyte derangement

Obesity is defined as BMI >30kg/m^2

Hypertension was defined as mean blood pressure ≥ 140/90mmHg or medical history of hypertension.

Diabetes was defined as medical history of diabetes or on diabetic treatment during study period.

Cigarette smoking- participants who have Cigarette smoking history at the start of the study

Alcohol consumption– participants who have alcohol consumption history at the start of the study

Herbal medication- participants who had ever taken any traditional healers.

4. RESULTS

4.1. Socio-demographic and Behavioral characteristics of the study participants

Among the total 816 staff members of EPHI, about 480 were volunteered to participate in the present study but 68 participants were excluding based on the eligibility criteria. A total of 412 study participants were met the inclusion criteria. More than half 211/412 (51.2%) of the study participant were males. The majority age group of the study participants were between 18-32 years accounting 169/412 (41.0%) followed by 33-47 years which was 163/412 (39.6%) and the rest with minimum number of participants were ≥ 48 years accounting 80/412 (19.4%) of the total study participants.

Regarding the marital status, about 247/412 (60.0%) of the study participants were married during the study period and the rest were never married or separated/widowed/divorced accounting 138/412 (33.5%) and 27/412 (6.6%) respectively. Regarding the educational background the majority 271/412 (65.8%) of the study participants had college and above educational background. Around 63/412 (15.3%) and 75/412 (18.2%) of the study participants attended secondary and primary school education respectively, the remaining 3/412 (0.7%) had no formal education.

The foremost study participants were never smoked cigarette or cigarette products which account 372/412 (90.3%). About 18/412 (4.4%) were smokers during the study period and the rest 22/412 (5.3%) were former smokers who stopped before the time of data collection. The majority of the study participants were alcohol drinkers which accounts 272/412 (66.0%) followed by non-drinkers accounting 140/412 (34.0%). In terms of khat chewing status, about 347/412 (84.2%), 18/412 (4.4%), and 47/412 (11.4%) of the study participants were non chewer, currently chewer, and former chewer during the study period respectively. The majority 406/412 (98.5%) of the study participants had no history of herbal medication use and the remaining 6/412 (1.5%) had been used traditional healers for different purpose at least once in life before the study period **(Table3).**

Table 4 Socio-demographic and Behavioral characteristics of the study participants (N=412), Addis Ababa, Ethiopia, 2018.

Characteristics		Total N	(%)
Sex	Male	211	51.2%
	Female	201	48.8%
Age group	18-32	169	41.0%
	33-47	163	39.6%
	≥48	80	19.4%
Marital status	Never married	138	33.5%
	Married	247	60.0%
	separated, widowed, divorced	27	6.6%
Educational background	no formal education	3	0.7%
	primary education	75	18.2%
	secondary education	63	15.3%
	college & above	271	65.8%
Quartiles of income per month	quartile1	104	25.2%
	quartile2	102	24.8%
	quartile3	103	25.0%
	quartile4	103	25.0%
Smoking status	Non smoker	372	90.3%
	Former smoker	22	5.3%
	Currently smoker	18	4.4%
Alcohol drinking status	Yes	272	66.0%
	No	140	34.0%
khat chewing status	Non chewer	347	84.2%
	Former chewer	47	11.4%
	Currently chewer	18	4.4%
Traditional medication	Yes	6	1.5%
	No	406	98.5%

Quartile1 was less than 1500 birr, quartile2= 1501-3173 birr, quartile3 = 3174-6676 birr, quartile4 was greater than 6676 birr. Former smoker and chewer were defined as those who smoke or chew before the time of data collection and stops during study period.

4.2. Clinical characteristics of the study participants

The finding showed that, 221/412 (53.6%) of the study participants had normal BMI value, the rest were under weight, overweight, and obese which accounts 24/412 (5.8%), 132/412 (32.0%), and 35/412 (8.5%) respectively. The majority of the study participants had normal systolic and diastolic blood pressure, accounting 342/412 (83.0%) and 318/412 (77.2%) respectively. About 68/412 (16.5%) by systolic and 87/412 (21.1%) by diastolic blood pressure were hypertensive during the study period. About 74/42 (18%) of the study participants had previous self-reported history of hypertension or on medication. About 14/412 (3.4%) and 22/412 (5.3%) of the study participants had previous self-reported history of diabetes and cardiovascular disease respectively during the time of data collection.

Only 157/412 (38.1%) of the study participants had previous kidney function test checkup and aware of their kidney function status during the study period. Among those, 48/157 (30.6%) had previous self-reported abnormality of kidney function test while 99/157(69.4%) had normal kidney function test. About 27/412 (6.6%) and 25/412 (6.1%) of the study participants had self-reported history of kidney stone and family history of renal failure respectively during the study period. The majority 356/412 (86.4%) of the study participants had no previous repeated exposure of urinary tract infection (UTI) and/or glomerulonephritis. The rest 56/412 (13.6%) had self-reported history of repeated UTI and/or glomerulonephritis (**Table4**).

Table 5 Clinical Characteristics of the study participants (N=412), Addis Ababa, Ethiopia, 2018.

Parameter		Total N	%
BMI	Under weight	24	5.8%
	normal	221	53.6%
	over weight	132	32.0%
	obese	35	8.5%
Mean systolic BP	Low	2	0.5%
	Normal	342	83.0%
	High	68	16.5%
Mean diastolic BP	Low	7	1.7%
	Normal	318	77.2%
	High	87	21.1%
History of hypertension	Yes	74	18.0%
	No	338	82.0%
History of diabetes	Yes	14	3.4%
	No	398	96.6%
History of CVD	Yes	22	5.3%
	No	390	94.7%
Previous kidney function test measurement	Yes	157	38.1%
	No	255	61.9%
Previous kidney function test abnormality	Yes	48	30.6%
	No	109	69.4%
History of kidney stone	Yes	27	6.6%
	No	385	93.4%
History of repeated UTI and/ or glomerulonephritis	Yes	56	13.6%
	No	356	86.4%
Family history of renal failure	Yes	25	6.1%
	No	387	93.9%

*BMI=body mass index was calculated by weight (kg)/ height (m^2). Mean systolic and diastolic BP (blood pressure) were evaluated by taking the average of three measurements. Low was ≤ 89/59, normal was between 90/60 – 139/89, and high or hypertension was ≥ 140/90 by systolic/diastolic respectively. Repeated UTI and/ or glomerulonephritis are defined as history of more than three times per year exposure of UTI and/ or glomerulonephritis. UTI=urinary tract infection, CVD=cardiovascular disease.

4.3. Assessment of kidney function tests of the study participants

Kidney function tests were measured for all study participants. The mean ± standard deviation (SD) of blood urea nitrogen (BUN) in the serum was 20.29 ± 6.23mg/dL respectively. Regarding to the serum creatinine level of the participants, the mean ± SD was 0.74 ± 0.17 mg/dL. The finding also showed that the study participant had the mean ± SD of urine creatinine was 144.42 ±74.41 mg/dL. The mean ± SD of estimated creatinine clearance test with MDRD and CKD-EPI equations was 132.67± 27.528mL/min/1.73m^2 and 131.03±23.017mL/min/1.73m^2 respectively among the total study participants.

The mean ± SD value of kidney function tests of female were 18.67±5.584mg/dL, 0.61±0.096mg/dL, and 117.78±60.485mg/dL, for BUN, serum creatinine, and urine creatinine respectively. The mean ± SD of BUN, serum creatinine, and urine creatinine for males were 21.84±6.433mg/dL, 0.86±0.134mg/dL, and 169.81±77.621mg/dL respectively. The mean GFR by MDRD and CKD-EPI equation for females was 140.31mmoL/min/1.73m^2 and 136.79mmoL/min/1.73m^2 respectively whereas about 125.38mmoL/min/1.73m^2 by MDRD and 125.54mmoL/min/1.73m^2 by CKD-EPI were for males **(Table5).**

Table 6 the mean ± standard deviation assessment of kidney function tests by gender (N=412), Addis Ababa, Ethiopia, 2018

Parameters		Gender		
	Total (N=412)	Male (N=211)	Female (N=201)	P-value
	Mean ± SD	Mean ± SD	Mean ± SD	<0.001
Urea	20.29±6.232	21.84±6.433	18.67±5.584	<0.001
serum creatinine	0.74±0.170	0.86±0.134	0.61±0.096	<0.001
urine creatinine	144.42±74.410	169.81±77.621	117.78±60.485	<0.001
eGFR by MDRD	132.67±27.528	125.38±25.064	140.31±27.982	<0.001
eGFR by CKD-EPI	131.03±23.017	125.54±16.442	136.79±27.197	<0.001

*Serum BUN and creatinine, and urine creatinine were measured by mg/dL. eGFR were through mmoL/min/1.73m^2. SD- standard deviation, BUN- blood urea nitrogen.

4.4. Prevalence of chronic kidney disease and kidney function Staging

As presented in figure 3, none of the study participants was in stage three, four, and five irrespective of the estimators we used. As we mentioned in the above, CKD is defined as GFR less than 60mL/min/1.73m^2 by both MDRD and CKD-EPI equation regardless of serum electrolytes. In the present study no one was in CKD or GFR less than 60mL/min/1.73m^{2,} but about 15/412 (3.6%) and 8/412 (1.9%) of the study participants were in stage two (GFR between 60-89 mL/min/1.73m^2) by using MDRD and CKD-EPI equations respectively. The remaining 397/412 (96.4%) by MDRD and 404/412 (98.1%) by CKD-EPI equation had normal kidney function (GFR ≥ 90mL/min/1.73m^2).

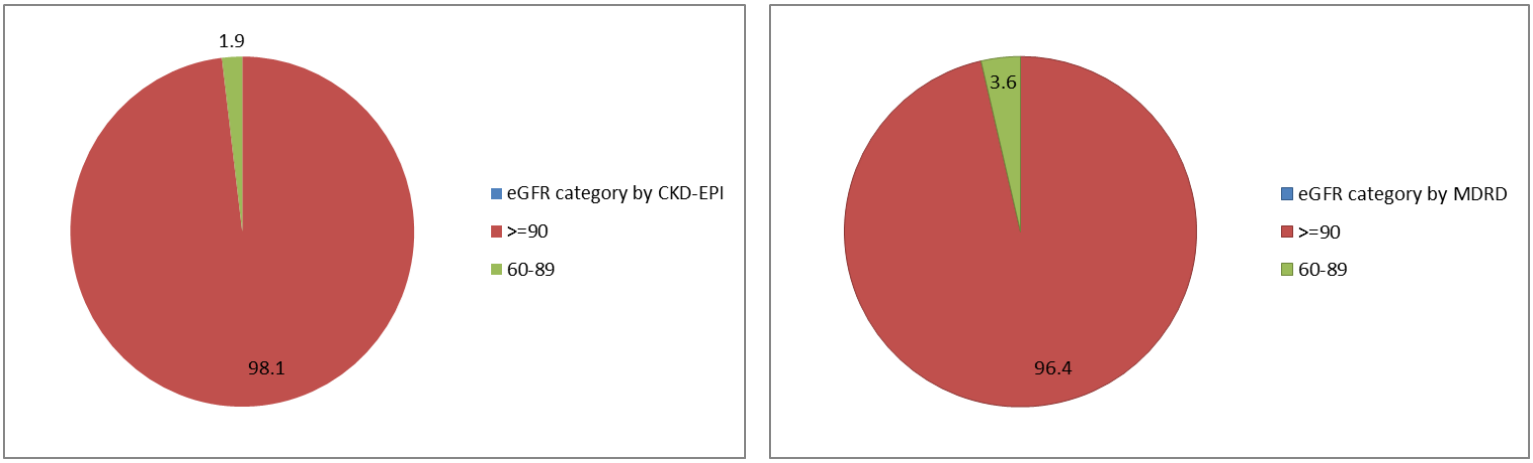


Figure 3. Pie chart to show the prevalence of CKD by MDRD and CKD-EPI equations of the study participants (N=412), Addis Ababa, Ethiopia, 2018.

*Normal kidney function was eGFR ≥ 90mL/min/1.73m^2, and stage two (G2) was eGFR between 60-89mL/min/1.73m^2, eGFR – estimated glomerular filtration rate.

4.5. Distribution of eGFR category by electrolyte level

According to our study results, the majority of the study participants had normal sodium value which was 402/412 (97.6%) while the remaining 10/412 (2.4%) were hypernatremia. No one was hyponatremiac in the study participants. All stage two (GFR between 60-89 mL/min/1.73 m^2) was among normal sodium level study participants which was 15/402(3.7%) and 8/402(2%) by MDRD and CKD-EPI equations respectively. No one was in stage two with hypernatremia regardless of the estimators used. Concerning the level of serum potassium, the prevalence of hypokalemia, normal, and hyperkalemia were 2/412 (0.5%), 371/412 (90%), and 39/412 (9.5%) respectively. All stage two was among normal potassium level nevertheless of the estimators.

Regarding the level of serum chloride, the prevalence of normal chloride predominate the study participants which was 388/412 (94.2%) whereas 2/412 (0.5%) and 22/412 (5.3%) were hypochloremia and hyperchloremia respectively. Among normal chloride value 373/388 (96.1%) and 15/388(3.9%) by MDRD as well as 380/388 (97.9%) and 8/388(2.1%) by CKD-EPI were normal kidney function and stage two respectively. No one was in stage two with hypochloremia and hyperchloremia irrespective of the estimators used.

Concerning serum calcium level, the foremost study participants had normal calcium value which accounts 376/412 (91.3%) while the remaining 35/412 (8.5%) and 1/412 (0.2%) was hypocalcemia and hypercalcaemia respectively. Among hypocalcemia participants about 3/35 (8.6%) by MDRD and 2/35 (5.7%) by CKD-EPI equations were stage two. The remaining 32/35 (91.4%) by MDRD and 33/35 (94.3%) by CKD-EPI had normal kidney function. About 12/376 (3.2%) and 6/376 (1.6%) by MDRD and CKD-EPI equations respectively was stage two with normal calcium value.

Regarding serum phosphate level, the majority 409/412 (99.3%) of the study participants had normal phosphate level while 3/412 (0.7%) was hyperphosphatemia. Among normal phosphate value, about 14/409 (3.4%) by MDRD equation and 8/409 (2.0%) by CKD-EPI were in stage two. About 1/3 (33.3%) by MDRD equation were in stage two among the hyperphosphatemia study participants whereas 2/3 (66.7%) had normal kidney function. The prevalence of hypomagnesaemia, normal magnesium, and hypermagnesaemia were 4/41 (1.0%), 407/412 (98.8%), and 1/412 (0.2%) respectively. All stage two (G2) regardless of the estimators used were among normal magnesium level study participants.

Table 7 Distribution of eGFR category using MDRD and CKD-EPI equations by electrolyte level (N=412), Addis Ababa, Ethiopia, 2018.

Serum electrolyte levels in mmol/L		Total participant N (%)	MDRD (GFR. mL/min/1.73 m2)		CKD-EPI (GFR. mL/min/1.73 m2)	
			≥90	60-89	≥90	60-90
			N (%)	N (%)	N (%)	N (%)
Sodium	Normal	402 (97.6)	387 (96.3)	15 (3.7)	394 (98)	8 (2.0)
	Hypernatremia	10 (2.4)	10 (100)	0 (0.0)	10 (100)	0 (0.0)
Potassium	Hypokalemia	2 (0.5)	2 (100)	0 (0.0)	2 (100)	0 (0.0)
	Normal	371 (90)	356 (96)	15 (4.0)	363 (97.8)	8 (2.2)
	Hyperkalemia	39 (9.5)	39 (100)	0 (0.0)	39 (100)	0 (0.0)
Chloride	Hypochloremia	2 (0.5)	2 (100.0)	0 (0.0)	2 (100)	0 (0.0)
	Normal	388 (94.2)	373(96.1)	15 (3.9)	380 (97.9)	8 (2.1)
	Hyperchloremia	22 (5.3)	22 (100)	0 (0.0)	22 (100)	0 (0.0)
Calcium	Hypocalcemia	35 (8.5)	32 (91.4)	3 (8.6)	33 (94.3)	2 (5.7)
	Normal	376 (91.3)	364 (96.8)	12 (3.2)	370 (98.4)	6 (1.6)
	Hypercalcaemia	1 (0.2)	1 (100)	0 (0.0)	1 (100)	0 (0.0)
Phosphate	Normal	409 (99.3)	395(96.6)	14 (3.4)	401 (98.0)	8 (2.0)
	Hyperphosphatemia	3 (0.7)	2 (66.7)	1 (33.3)	3 (100)	0 (0.0)
Magnesium	Hypomagnesaemia	4 (1.0)	4 (100)	0 (0.0)	4 (100.0)	0 (0.0)
	Normal	407 (98.8)	392(96.3)	15 (3.7)	399 (98.0)	8 (2.0)
	Hypermagnesaemia	1 (0.2)	1 (100)	0 (0.0)	1 (100)	0 (0.0)

*All serum electrolytes were measured through mmol/L. the normal value of each electrolyte level was as described on biochemical analysis. Normal/high kidney function is GFR ≥90mL/min/1.73m^2 by MDRD and/or CKD-EPI equations, stage two (G2) was GFR between 60-89mL/min/1.73m^2. eGFR –estimated glomerular filtration rate.

4.6. Associated factors of reduced GFR <90mL/min/1.73m^2

Table 7 and 8 depicts multinomial logistic analysis for reduced GFR (<90mL/min/1.73m^2) by MDRD equation using age, sex, marital status, income status, educational background, smoking status, alcohol drinking status, khat chewing status, BMI, blood pressure (systolic and diastolic BP), self-history of hypertension, diabetes, cardiovascular disease, kidney stone, and family history of kidney failure of the study participants as covariates. We did not analyze the multinomial logistic regression of the above variables by CKD-EPI equation because of minimal participants were under reduced GFR. In addition to this, the distribution of reduced GFR (<90mL/min/1.73m^2) or stage two kidney disease by the above variables was also performed by cross tabulation using both equations.

Older age, high BMI, and previous history of cardiovascular disease were statistically significant (P<0.05) variable associated with reduced GFR (<90mL/min/1.73m^2) by MDRD equation. Apart from this, there were no statistical evidence of association of reduced GFR (<90mL/min/1.73m^2) or stage two kidney disease by the other Socio-demographic, behavioral, and clinical characteristics mentioned above.

When we see the distribution of reduced GFR (<90mL/min/1.73m^2) by the above mentioned variables, the prevalence of reduced GFR (<90mL/min/1.73m^2) by age group was high for those who were at older age (≥48years) by both MDRD and CKD-EPI equations accounting 9(11.2%) and 5(6.2%) respectively. About 5(3.1%) and 3(1.8%) by MDRD and CKD-EPI equations respectively was prevalent at age group between 33-47 years. Only 1(0.6%) of the study participants at age group between 18-32 years was in stage two kidney disease by MDRD equation. No one was in stage two (G2) by CKD-EPI equation at this age group.

Males were more prevalent for reduced GFR (<90mL/min/1.73m^2) by both MDRD and CKD-EPI equations which was 11(5.2%) and 8(3.8%) respectively. About 4(2%) of females by MDRD equation were prevalent with reduced GFR. Regarding the marital status, the prevalence of stage two kidney disease or reduced GFR was 3(2.2%), 11(4.5%), and 1(3.7%) for never married, currently married, and separated/divorced/widowed respectively by MDRD equation. The prevalence by CKD-EPI was 2(1.4%) and 6(2.4%) for never married and currently married respectively. Concerning to the educational background of the study participants, the prevalence of reduced GFR was 5(6.7%), 1(1.6%), 9(3.3%) by MDRD equation and 2(2.7%), 1(1.6%),

5(1.8%) by CKD-EPI equation for primary school education, secondary school education, and college and above education respectively.

Regarding the income status, the prevalence of stage two kidney disease (GFR <90mL/min/1.73m^2) was 4(3.8%), 1(1.0%), 5(4.9%), and 5(4.9%) by MDRD and 1(1.0%), 1(1.0%), 4(3.9%), and 2(1.9%) by CKD-EPI equations was under quartile1,2,3,and 4 respectively. About 10(3.7%) and 6(2.2%) by MDRD and CKD-EPI respectively was in stage two kidney disease among alcohol drinkers. None of the study participants who used herbal medication was prevalent for stage two kidney disease (GFR <90mL/min/1.73m^2). The prevalence of reduced GFR or stage two kidney diseases was high among the smokers and chewer by both MDRD and CKD-EPI equations (**Table7**).

The prevalence of reduced GFR or stage two kidney diseases among the overweight/obese was 10(6%) and 6(3.6%) by MDRD and CKD-EPI equations respectively. About 3(4.8%) by MDRD and 2(3.2%) by CKD-EPI was under reduced GFR among the hypertensive study participants by systolic blood pressure (SBP). The prevalence of reduced GFR or stage two kidney diseases among normal SBP was 12(3.4%) and 6(1.7%) by MDRD and CKD-EPI equations respectively. Regarding to the diastolic blood pressure (DBP), the prevalence of reduced GFR or stage two kidney diseases was 2(2.6%) and 13(3.9%) by MDRD equation among the hypertensive and normal DBP of the study participants. None of the diastolic hypertensive participants were under reduced GFR or stage two kidney diseases by CKD-EPI equation. The prevalence of stage two kidney diseases (GFR < 90mL/min/1.73m^2) was 6(8.1%) and 3(4.1%) by MDRD and CKD-EPI equations respectively among self-reported hypertensive study participants.

Among the participants who had history of diabetes, about 1(7.1%) by MDRD equation was prevalent with reduced GFR (GFR < 90mL/min/1.73m^2) whereas no one was with it by CKD-EPI equation. The prevalence of reduced GFR among history of CVD was 2(9.1%) by MDRD equation. Regarding self-reported history of kidney stone, the prevalence of reduced GFR (GFR < 90mL/min/1.73m^2) was 2(7.4%) by both MDRD and CKD-EPI equations. None of the study participants who had history of repeated exposure of UTI and/glomerulonephritis were prevalent for reduced GFR. By both MDRD and CKD-EPI equations the prevalence of reduced GFR was 1(4%) among family history of kidney failure **(Table8).**

Table 8 Association of socio demographic and behavioral characteristics with reduced GFR (N=412), Addis Ababa, Ethiopia, 2018.

Characteristics	MDRD			CKD-EPI
	Distribution of reduced GFR (GFR <90 mL/min/1.73 m2)			Distribution of reduced GFR (GFR <90 mL/min/1.73 m2)
	N (%)	AOR (95% CI)	P-value	N (%)
18-32	1 (0.6)	1		0
33-47	5 (3.1)	3.435 (0.329 -35.901)	0.303	3 (1.8)
>=48	9 (11.2)	32.325 (2.732 - 382.442)	0.006	5 (6.2)
Female	4 (2.0)	1		0
Male	11 (5.2)	3.371 (0.656 - 17.325)	0.146	8 (3.8)
Single	3 (2.2)	1		2 (1.4)
Married	11 (4.5)	0.838 (0.164 - 4.295)	0.832	6 (2.4)
Separated/Widowed	1 (3.7)	0.454 (.026 - 7.841)	0.587	0
Primary school &less	5 (6.7)	1		2 (2.7)
Secondary	1 (1.6)	0.345(0.028 - 4.280)	0.408	1 (1.6)
>college &above	9 (3.3)	0.398 (0.061 - 2.599)	0.336	5 (1.8)
Quartile1	4 (3.8)	1		1 (1.0)
Quartile2	1 (1.0)	0.100 (0.007 - 1.413)	0.088	1 (1.0)
Quartile3	5 (4.9)	0.660 (0.078 - 5.605)	0.703	4 (3.9)
Quartile4	5 (4.9)	0.613 (0.071 - 5.276)	0.656	2 (1.9)
Never smoked	12 (3.2)	1		6 (1.6)
Smoker	3 (13.6)	0.744 (0.104 - 5.318)	0.768	2 (9.1)
Alcohol use				
No	5 (3.6)	1		2 (1.4)
Yes	10 (3.7)	0.593 (0.149 - 2.354)	0.458	6 (2.2)
Never chewed	11 (3.2)	1		5 (1.4)
Chewer	4 (8.5)	1.374 (0.228 - 8.266)	0.728	3 (6.4)
Herbal medication				
No	15 (3.7)	----------	----------	8 (2.0)
Yes	0			0

*P-value <0.05 was used as statically significant. AOR- adjusted odds ratio. Percentages were calculated based on the total number of participant. Smoker includes both the former and current smoker. Chewer includes both the former and current chewer.

Table 9 Association of the clinical characteristics with reduced GFR (N=412), Addis Ababa, Ethiopia, 2018.

Characteristics	MDRD			CKD-EPI
	Distribution of reduced GFR (GFR <90 mL/min/1.73 m2)			Distribution of reduced GFR (GFR <90 mL/min/1.73 m2)
	N (%)	AOR (95% CI)	P-value	N (%)
BMI				
<25kg/m^2	5 (2.0)	1		2 (0.8)
≥ 25kg/m^2	10 (6.0)	4.088 (1.032 - 16.192)	0.045	6 (3.6)
Mean systolic BP				
<140mmHg	12 (3.4)	1		6 (1.7)
≥140mmHg	3 (4.8)	0.440 (0.063 - 3.055)	0.406	2 (3.2)
Mean diastolic BP				
<90mmHg	13 (3.9)	1		8 (2.4)
≥90mmHg	2 (2.6)	0.387 (0.051 - 2.964)	0.361	0
History of HTN				
No	9 (2.7)	1		5 (1.5)
Yes	6 (8.1)	2.243 (0.576 - 8.727)	0.244	3 (4.1)
History of diabetes				
No	14 (3.5)	1		8 (2.0)
Yes	1 (7.1)	0.447 (0.036 - 5.555)	0.531	0
History of CVD				
No	13 (3.3)	1		8 (2.1)
Yes	2 (9.1)	8.378 (1.194 - 58.795)	0.033	0
History of kidney stone				
No	13 (3.4)	1		6 (1.6)
Yes	2 (7.4)	2.696 (0.425 - 17.112)	0.293	2 (7.4)
History of repeated UTI and/ or glomerulonephritis				
No	15 (4.2)	------	-------	8 (2.2)
Yes	0			0
Family history of renal failure				
No	14 (3.6)	1		7 (1.8)
Yes	1 (4.0)	1.788 (0.187 - 17.113)	0.614	1 (4.0)

*P-value <0.05 was used as statically significant. AOR- adjusted odds ratio. Percentages were calculated based on the total number of participant.

5. DISCUSSIONS

Chronic kidney disease (CKD) is one of the common chronic NCDs that characterized by persistent reduction of kidney function with or without structural abnormality of the kidney for more than three months (Levin *et al.*, 2013, Webster *et al.*, 2017). Mild to moderate kidney function reduction is more prevalent than ESRD (Keith *et al.*, 2004; Snyder and Pendergraph., 2005). However the worst side of CKD is asymptomatic nature and diagnosis at end stage, which is harsh and difficult to treat especially in developing counties (Baumgarten and Gehr, 2011). If untreated at early stage, it can result complications like electrolyte derangement, impairment of acid-base hemostasis, CVD with its adverse effect, anemia, hyperuricaemia, and CKD-MBD which are even fetal (Cirillo *et al.*, 2006; Levin *et al.*, 2013; Romagnani *et al.*, 2017; Thomas *et al.*, 2017). But can be prevented or delayed by appropriate medications and modification of life style (Levin *et al.*, 2013). So early screening and detection of CKD in the population to identify risk groups and risk minimization is the crucial step to reduce the morbidity and mortality rate of kidney failure and its complication. Globally, the incidence and prevalence increment of CKD is associated by different socio-demographic, behavioral, and co-morbid conditions (Hill *et al.*, 2016). Hypertension and diabetes are the two risk independent and major causative factors of kidney failure (Chen *et al.*, 2006; Hill *et al.*, 2016).

To our knowledge this was the first cross sectional, population-based study in Ethiopia on the prevalence of reduced GFR or chronic kidney disease and associated factors on the general population. Furthermore, detection of reduced GFR by estimating MDRD and CKD-EPI equations and their distribution with serum electrolyte were reported for the first time in Ethiopian population. Many researchers in the world reported various risk factors for the development of chronic kidney disease; our study also considered socio-demographic, behavioral, anthropometric, and clinical characteristics of the study participants. Initially our target was to analyze the association of risk factors with chronic kidney disease (GFR < 60mL/min/1.73m^2), but no one was under CKD. So we assessed the association of the risk factors with stage two (G2) kidney disease (GFR < 90mL/min/1.73m^2).

In this study half of the total EPHI staff members (412/816) were participated. We expected having this number of study participant may increase representativeness, although we selected the participants by voluntarism. When we see the socio-demographic, behavioral, and clinical

characteristics of the study participants, males (51.2%) predominate the proportion of females (48.8%) and most of these study participants were between age group of 18-33 years accounting more than fourty percent (41%). Most of the study participants were married (60%) during the study period and majority of these had college and above educational background (65.8%). Except alcohol drinking which accounts 66%, majority of the study participants did not practice bad behavioral characteristics such as smoking status (former smoker (5.3%) and current smoker (4.4%)), khat chewing status (former chewer (11.4%) and current chewer (4.4%)), and herbal medication accounting only 1.5% of the total study participants.

Low prevalence of bad behavioral characteristics may be due to good awareness of the study participants on their effect on health since most of them are health professionals. Some of the study participants also stop their practice after awareness. This is also supported by different researchers which stated that awareness is one of the major ways to minimize and prevent NCDs including CKD by reducing harmful behavioral practices (Arena *et al*., 2015; Ezzati *et al*., 2018). Actually defining alcohol drinking is one of the main obstacles to know the exact prevalence of it. In this study we defined as current drinker in any extent. The recent report (Khanal and Chataut., 2017) also showed that alcohol consumption as risk factor for NCDs regardless of amount and associated with smoking. Unfortunately in this study equal numbers of study participants (4.4%) were currently smokers and chewers during the study period. This may suggest that practicing more than one bad behavioral characteristic was common in our study participants which increase the chance of getting NCDs. Different researcher (Aikins *et al*., 2010; Arena *et al*., 2015; Rodrigues *et al*., 2016) also proves and states that using two and more different bad behavioral practice increases the chance of getting NCDs including CKD.

In our study clinically identified risk factors of CKD such as overweight, obesity, hypertension (by systolic, diastolic, or previous history), diabetes, CVD, family history of kidney failure, history of kidney stone, and repeated attack of UTI/glomerulonephritis were common in the study participants. Overweight (32%) and hypertension by diastolic (21.1%) were the two most common prevalent clinical characteristics in this study. Even the prevalence of hypertension by systolic and diastolic was not the same. This may be due to isolated hypertension occurrence in some study participants. In contrast to ours, one study showed that isolated systolic hypertension is more common than isolated diastolic hypertension (Tsimploulis *et al*., 2017). This may be due to the restriction of age in the study participants. The above study focuses on older age ≥65

years. By definition if somebody has blood pressure above the normal set point by systolic/diastolic, we call hypertension (Messerli *et al*., 2018). The prevalence of diabetes and CVD were relatively low which accounts 3.4% and 5.3% respectively. Even though the prevalence was low, their association with complications including CKD is very common unless they control early (Oluyombo *et al*., 2013; Gajjala *et al.*, 2015). Globally, more than two-third of CKD is caused by poor control of hypertension and diabetes (Chen *et al.*, 2006; Hill *et al.*, 2016). Other clinical and co-morbid conditions described above have also great effect on the progression of kidney function reduction which leads to kidney failure (Stanifer *et al*., 2014; Elhafeez *et al*., 2018).

Surprisingly the number of study participants that ever tested their kidney function status was low which accounts 38.1%, even though majority of these study participants are health workers and good access to checked it. So we can suggest that their awareness on kidney disease and its complication is not as such good in our study participants. In developing country lack of awareness on kidney failure is one of the major challenge to prevent and risk minimization of it (Elhafeez *et al*., 2018). One study done in Kinshasa, Democratic Republic of Congo on high risk groups also showed that only 12% of study participants were aware of their CKD which was 36% during the study period (Sumaili *et al*., 2009). Therefore working on knowledge, attitude, and practice of CKD and their risk factors are the key method to minimize the burden of it in the general population.

When we compare the mean kidney function tests by gender on the present study, females had lower BUN, serum creatinine, and urine creatinine than males which was 18.67mg/dL v 21.84mg/dL for BUN, 0.61mg/dL v 0.86mg/dL for serum creatinine, and 117.78mg/dL v 169.81mg/dL for urine creatinine respectively. But females had higher estimated creatinine clearance by both MDRD and CKD-EPI equations than males. The mean GFR by MDRD and CKD-EPI equations for females was 140.31mL/min/1.73m^2 and 136.79mL/min/1.73m^2 respectively whereas about 125.38mL/min/1.73m^2 by MDRD and 125.54mL/min/1.73m^2 by CKD-EPI were for males. The mean ± standard deviation of estimated creatinine clearance test was high with MDRD equation compared to CKD-EPI equation which was 132.67± 27.528mL/min/1.73m^2 and 131.03±23.017mL/min/1.73m^2 respectively among the total study participants.

Like that of ours, the Cameron study done on the prevalence and associated factors of CKD (Kaze *et al*., 2015) showed that the mean serum creatinine level was higher in males compared to females whereas the mean estimated GFR was lower in males irrespective of the estimators. This is because males are more muscular than females who stores and degrades more creatine phosphate (Brosnan *et al*., 2011). But the mean eGFR of our study which comprises 132.67mL/min/1.73m^2 and 131.03mL/min/1.73m^2 by MDRD and CKD-EPI equations respectively was higher than that of the above study (Kaze *et al*., 2015) which was 93.7 and 99.2 mL/min/1.73m^2 by MDRD and CKD-EPI equations respectively. The mean eGFR value of our study was also higher than the study done in India (Singh *et al*., 2013) on non-CKD group participants which was 116.94 mL/min/1.73m^2 by MDRD equation.

It was also far higher than the study done in Switzerland (Moulin *et al*., 2017) on the general population which showed that the mean eGFR was 98 mL/min/1.73m^2 by CKD-EPI equation. This variation could be due to the variation of the normal set point of eGFR in different countries population. In addition extreme outliers may affect the value which is the main drawback of measuring and comparing variables by their mean value. The mean blood urea and serum creatinine value of our study participant was a little bit lower than the above study done in Switzerland (Moulin *et al*., 2017) which revealed that the mean serum urea and creatinine value was 29.4mg/dL and 0.83mg/dL respectively.

We found that the prevalence of stage two kidney disease (GFR < 90mL/min/1.73m2) of the total study participants was 3.6% and 1.9% by MDRD and CKD-EPI equations respectively. Unlike the same study done in different countries, none of the study participants were on CKD (GFR < 60mL/min/1.73m^2) in the present study. The prevalence of CKD (GFR < 60mL/min/1.73m2) on the present study comprises zero which was far lower than the study done in India (Singh *et al*., 2013) that showed, the overall prevalence of CKD was 17.2% and 16.4% by MDRD and CKD-EPI equations respectively. But the result of stage two kidney disease (GFR< 90mL/min/1.73m2) on the present study was a little bit lower than it which was 4.3% and 3.2% by MDRD and CKD-EPI equations respectively.

Our finding was also lower than similar study done in southern Iran (Khajehdehi *et al*., 2014) which showed that, the overall prevalence of CKD (from stage 3 to 5) was 11.6% and the prevalence of stage1, 2, 3, 4, and 5 kidney disease was 8.5%, 66.1%, 11.4%, 0.1%, and 0.1%

respectively by MDRD equation, but not reported by CKD-EPI equation. The higher difference between the above two studies and the present study might be ethnic back ground difference, genetic variation, variation on the sample sizes, and variation of the sensitivity of the estimators used.

Another study done in Kinshasa (Democratic Republic of Congo) on selective risk groups, the prevalence of CKD found to be 36% (Sumaili *et al*., 2009) which was much higher than the present study, the prevalence was 4%, 6%, 18%, 2%, and 6% for stage 1,2,3,4, and 5 CKD respectively by MDRD equation. This higher difference with the current study could be mainly because of selective study population groups used, the Kinshasa researcher emphases the prevalence of CKD on diabetic, hypertensive, and obese patients. Our study result was also lower than that of sub-Saharan Africa country meta-analysis which revealed that the overall prevalence of CKD was 13.6% (Stanifer *et al*., 2014). The most difficult part to compare the present study with this meta-analysis was the difference of the estimators used. The meta-analysis done in sub-Saharan Africa country considers C-G equation and proteinuria in addition to MDRD and CKD-EPI equations to determine the prevalence of CKD.

The prevalence of CKD stages in our study was also far lower than the study done in southern Ethiopia which was 23.8% and 18.2 % of the study participants were under CKD by Cockcroft-Gault (C-G) and MDRD equations respectively (Fiseha *et al*., 2014). Even though the study was done in the same country, having the same cultural background, the major difference with the current study was restriction of study population. The southern Ethiopia study focuses on the prevalence of CKD and associated risk factors on the diabetic patients and did not consider other population groups. Another factor could be the difference of the estimators used. Different results displayed that, the prevalence of CKD and its staging can be varying even within analogous populations depending on the estimators used (Earley *et al*., 2012). CKD-EPI equation has been advised to get more accurate GFR in numerous African people, but practically not done (Elhafeez *et al*., 2018).

In contrast, our study findings was higher than the study done in Chennai, India for the screening of CKD on the general population and reported a decreased prevalence on kidney function test (eGFR <80 mL/min.m^2) that was 0.86% to 1.39% by C-G equation (Mani, 2005). But the major difference with the present study was variation of the cut point used for reduced filtration rate

and variation of estimators used. This is because of Cockcroft-Gault equation over estimates the filtration rate in contrast to MDRD equation which under estimates GFR especially when it is more than 60 mL per minute per 1.73 m^2 (Baumgarten and Gehr, 2011). CKD-EPI equation was the most recent and had lowest limitation compared to the former two (Levin *et al*., 2013). But the foremost studies done for screening of CKD in the world didn't consider CKD-EPI equation as major measurement tool (Hill *et al.*, 2016).

Measurement variation to estimate GFR is one of the major obstacles to know the exact prevalence and incidence rate of CKD in the globe (Hill *et al*., 2016). It also makes difficult to compare and contrast the studies done on chronic kidney disease. Even though we didn't get CKD on the present study, being stage two had higher risk to develop renal failure over time. The perspective follow up study done on kidney disease (Keith *et al*., 2004) showed that 1.1% of stage two participants developed end stage renal failure over five years which requires dialysis or kidney transplantation.

Our study also assessed the prevalence of electrolyte derangement and their distribution with eGFR using MDRD and CKD-EPI equations. Hyperkalemia was the most common electrolyte derangement encountered in the study participants which accounts 9.5%. Hypocalcemia was the second most common electrolyte disorder by 8.5% whereas no one was under hyponatremia and hypophosphatemia. This was in contrast to the similar study done in Netherland (Liamis *et al*., 2013) on the prevalence of electrolyte derangement and revealed as hyponatremia (7.7%) and hypernatremia (3.4%) was the most common electrolyte derangement whereas hyperkalemia was less common. This could be due to the restriction of age in the study participants. The Netherlands researcher focuses on the older age above 55years. The prevalence of hypomagnesaemia (1%) in our study was lower than the study done in Iran (Syedmoradi *et al*., 2011) which was (4.6%) and the above study done in Netherlands (Liamis *et al*., 2013) which accounts (2%). The reason might be methodology difference for the determination and sample processing of magnesium. In addition high prevalence of associated factors for hypomagnesaemia like diabetes may contribute for higher prevalence of it in the above two studies.

In the world, papers on electrolyte derangements were done most commonly in hospitalized patients and less likely to the general population. This makes difficult to compare and contrast

electrolyte disorder in the community. In our study hypernatremia (2.4%) was more prevalent than hyponatremia (0%), and hyperkalemia (9.5%) was far higher than hypokalemia (0.5%) in contrast to study done in Netherlands (Liamis *et al*., 2013) and in hospital admitted patients (Arampatzis *et al*., 2012). This may be due to high intake of sodium as salt and potassium in our study participants. The Ethiopian national survey also showed that our mean dietary salt intake is far higher than the recommended which was 8.3g/day (Challa *et al*., 2017). World Health Organization (WHO) recommends to take less than 5g/day of salt (WHO., 2012). In addition, in this study hypocalcemia (8.5%) was far higher than hypercalcaemia (0.2%), and hyperchloremia (5.3%) was higher than hypochloremia (0.5%). The commonest cause of hypocalcemia might be due to vitamin D deficiency and shortage of dietary calcium intake. In line to this study, the incidence of hypercalcaemia (4.7%) was lower than hypocalcemia (27.7%) in hospitalized patients (Catalano *et al*., 2018). Our finding was also supported by other review (Peacock., 2010) which showed that hypercalcemia is less likely encountered problem in the general population compared to hypocalcemia. Another study also showed that hypocalcemia can be manifested up to 1% in the general population (Frølich., 1998) which is comparable to the present study.

Most study participants under electrolyte derangement (except hypocalcemia and hyperphosphatemia) had normal GFR (GFR $\geq$ 90mL/min/1.73m^2) by both estimators. About 8.6% and 5.7% of hypocalcemia participants were stage two kidney diseases by MDRD and CKD-EPI equation respectively. One of the study participants from hyperphosphatemia was stage two kidney disease (GFR < 90mL/min/1.73m^2). Even though limited studies were done on the relationship between electrolyte derangement and kidney function test in the general population, CKD development is one of the major causes for electrolyte derangement (Dhondup and Qian., 2017). CKD progression leads to further deterioration of electrolyte derangement. Electrolyte disorder in CKD is one of the indications for kidney tubular damage and it is common when CKD transforms into end stage kidney failure (Levin *et al*., 2013). In our study participants no one was under serious kidney disease and the result showed that electrolyte derangement was less likely associated with reduced glomerular filtration rate.

In this study older age, high BMI, and previous history of cardiovascular disease were the factors found to be significantly associated with stage two kidney disease (P=0.006), (P=0.045), and (P=0.033) respectively after adjustment. The association of older age with reduced glomerular filtration rate in the present study was in line with other studies done in South West Nigeria

(Oluyombo *et al*., 2013), in India (Singh *et al*., 2013), and in China (Zhang *et al.*, 2018). But this association was in contrast to the study done in South Africa (Matsha et al., 2013) which revealed that younger age between 20-50 years were more prevalent for CKD than the older age groups. Meta-analysis on sub Saharan country population (Stanifer *et al*., 2014) on the prevalence and associated factors of CKD also showed that younger age were the most affected groups with CKD which makes it more serious in this area. This variation could be due to the increment of other risk factors like hypertension, diabetes mellitus, and retroviral infection during young age.

Like that of ours, high BMI which indicates the obesity status of the population were one of the contributing factor for reduced glomerular filtration rate on the same study done in Saudi (Emem-Chioma *et al.*, 2011) in southern Iran (Khajehdehi *et al.*, 2014), and in China (Zhang *et al.*, 2018). One systematic review also showed that strong association between weight loss through dietary restriction and exercise with improving of kidney function tests (Afshinnia *et al*., 2009). The exact molecular mechanism of obesity related renal injury or dysfunction is not well understood but supposed to be due to change of hemodynamic stability, metabolic disorder, activation of inflammatory process, and glomerular hyper filtration (Hall *et al.,* 2014). obesity particularly visceral obesity leads to hemodynamic instability by hyper activation of the sympathetic nervous system and renin angiotensin aldosterone system, and increasing renal tubular sodium reabsorption resulting in hypertension which is one of the major contributing factor for CKD (Hall *et al*., 2002; Slee., 2012).

Even though obesity can mostly contribute to the development of CKD through hypertension and diabetes; the two major causative factor of CKD, there is also an evidence that hypertension or diabetes independent association of renal dysfunction/ CKD (Ejerblad *et al*., 2006). Renal dysfunction can be directly resulted due to the accumulation of ectopic fats in and around the kidney (Hall *et al.,* 2014). During obesity ectopic lipid accumulation can happen in non-adipose tissues like kidney (Ejerblad *et al*., 2006). This leads to excessive production of toxic lipid metabolites, such as ceramides and diacylglycerols in non-adipose tissue cells. These toxic metabolites can lead to renal dysfunction or injury through mitochondrial dysfunction and endoplasmic reticulum stress (Unger and Scherer., 2010).

Another associated factor with reduced glomerular filtration rate in our study was previous history of CVD. This is in line with systematic review done by (Kazory and Ross., 2009; Gajjala *et al.*, 2015; Schefold *et al*., 2016; Elhafeez *et al*., 2018) which showed that CKD and CVD are interdependent to each other (CKD is a risk factor for CVD and the reverse is also true). Chronic kidney disease increases risk of getting CVD by two to four times in the general population (Gansevoort *et al.,* 2013). Even though the exact molecular mechanism is not well understood, some of the metabolic pathway that interrelate CVD and CKD are hyperactivity of RAAS, inflammation, osmotic sodium retention, endothelial dysfunction, dyslipidemia, and phosphatidylinositol 3-kinase (PI 3-kinase)-dependent signaling pathways (Gajjala *et al.*, 2015). In addition CKD and CVD shares common risk factors, such as smoking, obesity, hypertension, diabetes mellitus, and dyslipidemia, which may contribute to the occurrence of CVD along with CKD.

Unlike meta-analysis done on United States of America (Baumgarten and Gehr., 2011), on African (Elhafeez *et al*., 2018), and on sub Saharan country (Stanifer *et al*., 2014) sex, smoking status, history of hypertension or current diagnosis of it, history of diabetes, family history of CKD, kidney stone, income status, educational background, and other variables that considered as risk factors of CKD, were not significantly associated with reduced filtration rate in the present study. This might be due to less number of study participants were in stage two (GFR < 90mL/min/1.73m2) which was less reliable to show the association of risk factors. Other reason could be due to short duration occurrence of the risk factors like hypertension, and diabetes or the well-controlled status of those diseases in our study participants. We did not perform the association of herbal medication use and repeated UTI/glomerulonephritis with stage two (G2) kidney disease. This was because none of the study participants that used herbal medication or that diagnosed by repeated UTI/glomerulonephritis were under stage two.

According to the researches done in Saudi Arabia (Alsuwaida *et al*., 2010), in Beijing (Li *et al*., 2006), and in South West Nigeria (Oluyombo *et al*., 2013) diabetes and hypertension were the two risk independent factors for reduced GFR or CKD. In contrary to this, we did not get significant association between history of diabetes or hypertension with reduced GFR. But we found that the prevalence of decreased GFR was higher from self-reported diabetes (7.1%) and hypertension (8.1%) than non-diseased study participants.

6. CONCLUSION

In this cross-sectional based study for early detection and screening of CKD, we found that 3.6% and 1.9% stage two kidney disease by MDRD and CKD-EPI equations respectively. None of the study participants were under critical kidney disease or GFR<60mmoL/min/1.73m^2. But clinically identified risk factors like hypertension, diabetes, CVD, obesity, and family history of kidney failure were common in the study participants which comprise 18%, 3.4%, 5.3%, 8.5%, and 6.1% respectively. Older age, high BMI, and previous history of cardiovascular disease were significantly associated factors for reduced glomerular filtration rate. Except Hyponatremia and hypophosphatemia, all electrolyte derangements were encountered in the study participants. Hyperkalemia (9.5%) and hypocalcemia (8.5%) were the most electrolyte disorders come across from the study participants. Even though the prevalence of kidney disease was relatively low, early detection and screening of CKD should be practice in order to prevent and minimize end stage renal failure. The knowledge gained from this study could be a big input for health professionals, policy makers, and the community for risk minimization of end stage renal failure.

7. STRENGTH AND LIMITATION OF THE STUDY

Strength of the study

- It was the first study for screening of CKD on the general population in Ethiopia.
- Data collection was done through digital system which aids to save the data for further investigation.
- We had relatively reduced the experimental errors since we analyzed the blood and urine samples by COBAS 6000 analyzer.

Limitation of the study

- The study was restricted among Ethiopian Public Health Institute Staff Members which did not give over all conclusions for Ethiopian population.
- The study participants were chosen based on non-random sampling technique.
- The study was cross sectional based and we measured serum creatinine only once for each participant which could overestimate the filtration rate, so it was better to measure more than once .
- We relied on MDRD and CKD-EPI equations to determine the prevalence of CKD. But there is no evidence for the validation of these equations among Ethiopian population.

8. RECOMMENDATION

- Screening and early detection of CKD for high risk groups like older age, high BMI, and history of CVD should be practice to prevent the adverse outcomes of it.
- Even though the prevalence of kidney disease was low, further prospective follow up studies might be needed to clearly address the exact prevalence of chronic kidney disease and their associated factors.
- The research area was restricted at Ethiopian Public Health Institute which did not explore the general population of Ethiopia other than Ethiopian Public Health Institute. Therefore increasing the study area will bring overall prevalence and associated factors of chronic kidney disease in Ethiopian population.
- Due to limitation of reagent availability, albuminuria was not done on the study participants. There is a necessity for measurement of albuminuria to detect kidney damage since creatinine measurement only shows the capacity of functional status of kidney. So further study may be needed to show both the functional status and cellular damage of kidney by assessing both glomerular filtration rate and albuminuria.

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Annex I: Information sheet (English version)

Information sheet for the participants of the study entitled assessment of serum electrolyte and kidney function tests among Ethiopian public health institute (EPHI) staff members.

Addis Ababa University, school of medicine, department of biochemistry

Principal investigator: Meseret Derbew

Advisors:

Dr. Daniel Seifu

Dr. Maria T/mariam

Mr. Abebe Bekele

Name of sponsors: Ethiopian Public Health Institute and Addis Ababa University

1. **Aim of the study**

This information sheet is prepared for a project with the aim of screening and early detection of CKD by assessing serum electrolytes and kidney function tests and to detect the associated risk factors for CKD among Ethiopian public health institute (EPHI) staff members.

2. **Study design and procedure**

If you agree to take part in this study, you will be given the consent form to sign, and interviewed by health professional to assess whether you qualify to participate in the study or not. If you are fit for the study, the data collector will be asked some questions about the socio-demographic characteristics and risk factors of chronic kidney disease. Physical measurements like weight, height, and blood pressure will be taken. 5mL of blood sample will be also collected for laboratory examination of serum electrolyte and kidney function tests. eGFR will be calculated using serum creatinine by MDRD and CKD-EPI equation.

3. **Risks**

Participating in this project will not cause more discomfort than the routine examination you required during clinic visit. But minor pain and skin color change may be occur following blood drawing, which will disappear within short duration. The amount of blood required in the study is 5mL, which will not affect your health. The whole procedure will be carried out by health professionals through standard clinical practice, so participating in this study has no major risks.

4. **Benefits**

Participating in this study is invented to show the magnitude of invisible epidemics of chronic kidney disease and it will give benefit through early screening and early identification of risk factors for CKD for which you will be advised for further clinical follow up. You will have the chance to know your general health status from the project without any direct incentive. The cost will be covered by the project.

5. **Confidentiality**

All information about the participant will be kept confidential. Logbooks used in the laboratory will have no names but codes. The information sheet that links the coded number to participant name will be locked inside a box and it will not be revealed to anyone except your principal investigator.

6. **Right to refuse**

You have full of right to withdraw from participating in this study at any time before and after the consent without explaining the reason.

Annex II: Informed consent (English Version)

Code number_____

Study participant name_____

Study participant signature_____

I have been informed about the study, which plans to assess serum electrolyte and kidney function test among EPHI staff members. The objective and the application of the study were explained to me. I am also informed that all information about the participant will be kept confidential and the right to withdraw from the study any time. I had also the right to ask a question and suggestion about the project. I was also told that the result of the laboratory test would be reported to me if I need it. It is therefore I voluntarily agreed the informed consent with full understanding of the research. I voluntarily answered the prepared question and give my blood for the aforementioned study. I, the under signed, confirm that, as I give consent to participate in the study; it is with a clear understanding of the objectives and the study conditions.

I _____ do hereby give consent to Dr./Mr./Mrs./Miss_____ to include me in the proposed research.

Signature Date

Participant: _____ _____

Interviewer: _____ _____

Annex III: Questionnaires (English Version)

Code_____

1. **Socio-demographic**

no	Variables	Response
01	Age	_____year
02	Sex	1.male 2.female
02	Marital status	1.Never married 2.Currently married 3.Separated/ Divorced/Widowed
03	Ethnic background	_____
04	Education	1.No education 2.primery 3.Secondary 4.college/university and above
05	Occupation	1. Unemployed 2.Government 3.Nongovernment 4. Private
06	Income per month	_____birr
07	Religion	1.Orthodox 2.Muslim 3.Protestant 4.Catholic 5.Others

2. **Behavioral**

08	Smoking status	1. Never smoke 2. Former smoke 3. Currently smoke
09	If you smoke currently, how long ago you first started smoking?	_____
10	On average, how many times do you smoke each day?	_____
11	If you were former smoker, How long ago did you stop smoking?	_____
12	Alcohol Consumption status	1. Never drink 2. Former drink 3. Currently drink
14	What type of alcohol do you drink?	_____
15	How many standard units of alcohol do you drink per day?	1. Less than one 2. One-Three 3. Four –Six 4. More than six
21	Have you ever seen a traditional healer for treatment of diseases?	1. Yes 2. No

History of kidney disease and comorbidities

No.	Question	Response
30	Have you ever had your kidney function test measured?	1. Yes 2. No
31	Have you ever been told that you have reduction of kidney function?	1. Yes 2. No
32	Have you been told in the past 03 months?	1. Yes 2. No
33	Have you ever been told that you have kidney stone? If yes, when _____	1. Yes 2. No
34	Have you repeated UTI and/ or glomerulonephritis? If yes, how many times per year_____	1. Yes 2. No
36	Have you ever seen a traditional healer for kidney disease? If yes, when_____	1. Yes 2. No
37	Are you currently taking any herbal or traditional remedy for your kidney disease, infection or other disease?	1. Yes 2. No
38	Family history of kidney failure? If yes, who_____	1. Yes 2. No
38	Which of the following co-morbid conditions do you had?	1. Hypertension 2. DM 3. CVD 4. Obesity 5. Other
39	If there is co-morbid condition, medication history of it	_____

Annex IV Anthropometric and biochemical measurements

Anthropometric measurements

1. Height _____cm
2. Weight _____kg
3. BMI _____kg/m^2
4. Mean blood pressure _____mmHg

Biochemical measurements

1. Serum sodium _____mg/dL
2. Serum potassium _____mg/dL
3. Serum chloride _____mg/dL
4. Serum calcium _____mg/dL
5. Serum magnesium _____mg/dL
6. Serum phosphate _____mg/dL
7. Serum urea/ BUN _____mg/dL
8. Serum creatinine _____mg/dL
9. Urine creatinine _____mg/dL
10. eGFR

    Using MDRD equation _____mL/min/1.73m^2

    Using CKD-EPI equation _____ mL/min/1.73m^2