ADDIS ABABA UNIVERSITY

COLLEGE OF HEALTH SCIENCES

DEPARTMENT OF INTERNAL MEDICINE

Magnitude and patterns of biochemical mineral bone disease abnormalities among predialysis patients with CKD in TASH renal clinic, 2012 E.C.

Principal Investigator:Sirak Melkeneh (MD, Internal Medicine Resident)

A Thesis to be submitted to the Department of Internal Medicine, School of Medicine, College of Health Sciences, Addis Ababa University, in partial fulfillment of the Specialty Certificate in Internal Medicine

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Abbreviations and acronyms

1,25(OH)2D - 1,25-dihydroxyvitamin D

25(OH)D - 25-hydroxyvitamin D

P – Phosphate

Ca - Calcium

ALP - Alkaline phosphates

BMD - Bone mineral density

CAC - Coronary artery calcification

CKD□MBD – Chronic kidney disease mineral and bone disorder

CI - Confidence interval

CT - Computed tomography

DXA - Dual-energy X-ray absorptiometry

eGFR - Estimated glomerular filtration rate

FGF - Fibroblast growth factor

HD - Hemodialysis

iPTH - Intact parathyroid hormone

SHPT – Secondary Hyperparathyroidism

KDIGO - Kidney Disease: Improving Global Outcomes

KDOQI - Kidney Disease Outcomes Quality Initiative

LVH - Left ventricular hypertrophy

MRI - Magnetic resonance imaging

OR – Odds Ratio

SD - Standard deviation

Abstract

Background: Mineral bone disease (MBD) abnormalities are common complications in patients with kidney disease. MBD abnormalities in chronic kidney disease (CKD)patientsare referred to as CKD-MBD; the abnormalities could be biochemical, structural changes of the bone, or both. These abnormalities are known to be associated with increased morbidity and mortality. In spite of their importance, there is limited data on CKD-MBD abnormalities in Ethiopia. This study looked in to the magnitude and factors associated with biochemical CKD-MBD abnormalities among predialysis CKD patients following in a single center in Ethiopia.

Objective: The major objective of the study is to determine the magnitude of biochemical mineral bone disease abnormalities; namely, serum calcium, phosphorus and parathyroid hormone levels. Additionally factors associated with these biochemical parameters and the management practices are assessed.

Methods: This isa cross-sectional study. One hundred consecutive patients who havehad follow-up for at least 6 months and eGFRless than 60ml/min/1.73m^2 using CKD- EPI equation were included in this study. Serum calcium, albumin, phosphorusand PTHlevels weredetermined. Demographic and clinical data were collected using a structured questionnaire.IBM SPSS software version26 was used for analysis.

Results: The mean age of the patients was 54 with the range of 18 – 92. The male to female ratio is 2.7:1. Patients with stages 3a, 3b, 4 and 5 CKD contributed to 23%, 29%, 26% and 22% of the total respectively. The main causes of CKD were diabetes and hypertension. From the total of 100 patients 31% had hyperphosphatemia,36% hypocalcemia, and 89% had hyperparathyroidism.Estimated GFR correlated negatively with serum PTHlevel but correlated positively with serum calcium level.During a six month follow up period serum calcium and phosphorus were determined at least once in 61% and 62% of patients while serum PTH level wasdetermined in 15% of the patients. Among patients who require treatment according to evidenced based guidelines directed to each biochemical CKD-MBD abnormalities, prescription was given to30% patients for hyperphosphatemia, 38% for those with hypocalcemia, and45% for patients with hyperparathyroidism.

Conclusion: Hypocalcemia, hyperparathyroidism, and hyperphosphatemia are common biochemical CKD-MBD abnormalities among predialysis CKD patients following in the renal clinic of TikurAnbessa specialized hospital, Addis Ababa, Ethiopia.

Introduction

Background

Chronic kidney disease (CKD) constitutes a public health problem that is estimated to affect more than 10% ofthe global population, and the prevalence of which has increased in recent years.[1]The pooled prevalence ofCKD is 10.1% in the general population, 24.7% in hypertensive, and 16.6% among diabetes mellitus patients in Africa.[2]The prevalence of CKD was 26%among hypertensive and diabetes mellitus patients in Ethiopia. [3]Based on the 2012 KDIGO guideline, CKD is defined as abnormalities of kidney structure or function, present for >3 months, with implications for health.[4]It also classifies it according to severity from stages 1-5.

Bone mineral metabolism abnormalities that occur in CKD patients are recently defined inKDIGO guidelines as CKD‐mineral and bone disorder (CKD‐MBD).[5]CKD‐MBD is a systemic disorder that is characterized by abnormal calcium, phosphorous, PTH, and Vitamin D metabolism, which, in addition to affecting the skeletal system, is related to the appearance of cardiovascular and soft tissue calcifications that in turn are associated with cardiovascular pathologies in patients with CKD. The biochemical abnormalities are common in CKD and are the primary indicators by which the diagnosis and management of CKD‐MBD is made.

Bone abnormalities are found almost universally in patients with CKD stage 5 and in majority of patients with stages 3-5.The biochemical abnormalities form the primary routine indicators in management ofCKD-MBD, though there are limitations. Furthermore, KDIGO recently suggests to perform a bone biopsy only if knowledge of the type of renal osteodystrophy will impact treatment decisions and to do BMD testing to assess fracture risk patients only in patients with evidence of CKD-MBD and/or risk factors for osteoporosis. [5]

Patients with chronic kidney disease (CKD) are at an increased risk for bone fractures. Fracture prevalence rates are more than 2-fold higher when glomerular filtration rate (GFR) is less than compared to when is greater than 60 mL/ min/1.73m2and fracture risk increases further as kidney function declines.[67]

The bone mineral metabolism abnormalities start during first stages of CKD as renal function decreases, long before the need for renal replacement therapy and can be positively or negatively influenced by the treatment strategy employed. Elevated PTH and hyperphosphatemia were

recently identified again as risk factors for mortality in dialysis patients.[89]Elevated serum phosphate levels were independently associated with increased mortality risk among this population of patients with CKD.[10]As such, it is recommended that attending physicians monitor and control biochemical parameters early in the development of CKD,before the need fordialysis.[5]

Statement of the problem

Bone abnormalities are found almost universally in patients with CKD stage 5 and in majority of patients with stages 3-5. The biochemical abnormalities form the primary routine indicators in management of CKD-MBD, though there are limitations. Patients with chronic kidney disease (CKD) are at an increased risk for bone fractures, increased CVD mortality.

Significance of the study

Despite the high prevalence of MBDs inCKD patients, there is no data on CKD□MBD from Ethiopia.Even the practice of CKD□MBD is from guidelines which are based on Western data and expert suggestions. Because of the paucity of data from our countryan urgent need for a study in this area was felt to fill the knowledge gap.Therefore, a study to investigate the prevalence of MBD in CKD patients was done to know the prevalence of the abnormalities and identify gaps in management.

Literature Review

CKD is defined according to KDIGO as structural or functional abnormalities of the kidney that persist for at least 3 months and is manifested by either kidney damage (most frequentlydetected as persistent albuminuria or proteinuria (> 30 mg/ 24h or > 1 on specific dipstick); or a decreased glomerular filtration rate (GFR), (< 60 mL/min per 1.73 m2).[4]KDIGO defined CKD-MBD as a systemic disorder of mineral and bone metabolism due to CKD, manifested by either one or a combination of the following three components:Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism, Abnormalities in bone turnover, mineralization volume linear growth, or strength or Extraskeletal (Vascular or other soft tissue) calcification.[5]

Chronic kidney disease (CKD) constitutes a public health problem that is estimated to affect more than 10% ofthe global population, and the prevalence of which has increased in recent years.[1]The pooled prevalence ofCKD is 10.1% in the general population, 24.7% in hypertensive, and 16.6% among diabetes mellitus patients in Africa.[2] In our case there is limited data on CKD but a study conducted at Jimma showed the prevalence of CKD is 26% (95% CI; 20.3%-31.8%) and the predictors of CKD were uncontrolled blood pressure, fasting blood sugar> 150mg/dl, long duration of hypertension, ACEIs nonusers, and poor knowledge about CKD.[3]

The bone mineral metabolism abnormalities start during first stages of CKD as renal function decreases, long before the need for renal replacement therapy. Even though there is limited data available in our country but According to study done in Nigeria, the prevalence of various mineral bone disease abnormalities were 70% hyperphosphatemia, 85% hyperparathyroidism, and 100% low levels of 25 (OH) D.[11]

According to KDIGO the term renal osteodystrophy is exclusively used to define bone pathology observed on biopsyand using the TMV system classified as: Osteitis fibrosa cystica characterized predominantly by high turnover due to secondary hyperparathyroidism, Adynamic bone disease characterized predominantly by low turnover, Osteomalacia characterized by low bone turnover in combination with abnormal mineralization, Mixed uremic osteodystrophy characterized by either high- or low-bone turnover and by abnormal mineralization.[5]

The pathophysiology behind secondary hyperparathyroidism and the consequent high-turnover bone disease is through the following events: (1) declining GFR leads to reduced excretion of phosphate and, thus, phosphate retention; (2) the retained phosphate stimulates increased synthesis of both FGF-23 by osteocytes and PTH and stimulates growth of parathyroid gland mass; and (3) decreased levels of ionized calcium, resulting from suppression of calcitriol production by FGF-23 and by the failing kidney, as well as phosphate retention, also stimulate PTH production. Low calcitriol levels contribute to hyperparathyroidism, both by leading to hypocalcemia and also by a direct effect on PTH gene transcription. These changes start to occur when the GFR falls below 60 mL/min.

The importance of discussing about CKD- MBD is because of its complications mainly bone fractures, Extra skeletal calcifications and increased CVD mortality.

It is well established that patients with CKD G3a–G5D have increased fracture rates compared with the general population, and moreover, incident hip fractures are associated with substantial morbidity and mortality[7]. In study done in Canada the prevalence of clinical fracture were 14.3% of GFR categories G3a and G3b, 15.7% of GFR category G4, and 19.7% of GFR category. [12]KDIGO suggested to do BMD testing to assess fracture risk in patients with evidence of CKD-MBD and/or risk factors for osteoporosisif results will impact treatment decisions. [5]

Extraskeletal calcification is common in patients with CKD, particularly those on dialysis.[13]Vascular calcification is associated with cardiovascular disease (CVD), which is the most common cause of death in CKD. This may be due in part to excess vascular (arterial) calcification, particularly coronary artery calcification (CAC), which can be observed even in very young dialysis patients, who lack the typical vascular damage risk factors of hypertension, dyslipidemia, and smoking. Calcium can be deposited into either or both of the medial or intimal layers of the vasculature.[1415]The high prevalence of vascular calcifications among CKD patients is related to the administration of calcium-containing phosphate binders used to treat hyperphosphatemia. Besides arteries valvular calcifications can occur. KDIGO advises In patients with CKD G3a–G5D, that a lateral abdominal radiograph can be used to detect the presence or absence of vascular calcification, and an echocardiogram can be used to detect the

presence or absence of valvular calcification and patients with calcifications to be considered at highest cardiovascular risk.[5]

Bone abnormalities are found almost universally in patients with CKD stage 5 and in majority of patients with stages 3-5.[16] The biochemical abnormalities form the primary routine indicators in management of CKD-MBD, though there are limitations. Diagnosis for CKD-MBD using the invasive bone biopsy for bone turnover, mineralization, and volume; or arterial, valvular or coronary calcification score using gold standards such as electron beam CT, or multi-slice CT; or measuring bone mineral density (BMD) by Z score of dual energy X ray absorptiometry (DXA), ultrasound or echocardiography to assess tissue calcification, are not necessary in routine clinical practice especially in a developing country as ours. Therefore, changes in se- rum calcium, phosphorus, PTH, 25 (OH) D, and total alkaline phosphatase were used in this work to assess CKD-MBD in the study group. According to KDIGO also most of the interventions targeted at CKD -MBD is using medications that maintain the serum levels of Calcium, PTH, Phosphorus and Vit D.[5]

However, despite high prevalence of MBDs in CKD patients, there are no data on CKD‐MBD from Ethiopia. Even the practice of CKD‐MBD is from guidelines which are based on Western data and expert suggestions, due to paucity of data from the country and an urgent need for studies in this area was felt to fill the knowledge gap. Therefore, a prospective study using the biochemical methods to investigate the prevalence of MBD in CKD patients at our center was performed.

Objectives

General Objective:

- Magnitude and patterns of biochemical Mineral Bone Disease abnormalities among predialysis patients with Chronic Kidney Disease in TASH renal clinic, 2012 E.C.

Specific objectives:

- To determine the magnitude and patterns of abnormalities in serum Calcium, Phosphate and PTH levels among predialysis patients (Stage 3-5) with Chronic Kidney Disease.
- To identify risk factors associated with Chronic Kidney Disease-Mineral Bone Disease
- To identify gaps in the current practice

Method

• **Study Setting:**The Study wasconducted in the renal clinic of TASH on patients who have CKD follow-up.

• **Study design:**The study is cross-sectional, single center one

- **Study Period:** July 1 – September 30, 2020
- **Study population:** The source population includes consecutive patients who are ≥ 18yrs of age and have eGFR of < 60 ml/min/1.73m2 for at least 03 months and have follow-up at renal clinic for at least 06 months. Those patientswho have Stage 3-5 CKD by estimating GFR using CKD-EQI equation are included in the study. Patients with these characteristics were excluded: patients on dialysis, patients who have primary hyperparathyroidism or undergone parathyroid surgery and patients who are taking Calcium supplements over the counter.

•**Sample size:**100 using the finite formula with Confidence level of 95%, 5% margin of error, Sample population believed to be 80%, and source population of 180.

•**Data collection and sampling procedures:**Patients who have serum creatine ≥ 1.3mg/dl from their previous lab results were selected for estimation of their GFR using CKD-EPI equation.

- If their GFR is < 60 ml/min/1.73m2 they are qualified for the study, informed consent was taken and data collected using structured questionnaire by a nurse.
- The blood samples were collected by a nurse, centrifuged, stored in a deep freezer with -30◦C for about a week then were taken to EPHI Laboratory for analysis.
- Serum Calcium and Phosphorus were assayed at EPHI using ion-selective electrode method. PTH was done at EPHI using Electrochemiluminescence immunoassay. Serum albumin was done using Photometric method at EPHI.
- To identify the gaps in practice and risk factors the patients I- care number from the questionnaire was used to review their previous history.

- **Dependent Variables:** Serum Calcium, Serum Phosphate and Serum PTH
- **Independent Variables:**
    - Age, sex, BMI, Blood pressure, place of residence, educational status, marital status, occupation, medical comorbidity, smoking hx

- eGFR
- Cause of CKD
- Urine dipstick protein
- Abdominal U/S finding
- CKD- MBD treatment status

•**Operational definitions:**In accordance with KDIGO guidelines:

CKD: serum creatinine level above laboratory baseline for sex for more than 03 months.

Stage 1 CKD: Estimated GFR above 90 ml/min/1.73m2

Stage 2 CKD: Estimated GFR b/n 90 and 60 ml/min/1.73m2

Stage 3A CKD: Estimated GFR b/n 59 and 45 ml/min/1.73m2

Stage 3B CKD: Estimated GFR b/n 44 and 30 ml/min/1.73m2

Stage 4 CKD: Estimated GFR b/n 29 and 15 ml/min/1.73m2

Stage 5 CKD: Estimated GFR less than 15 ml/min/1.73m2

Stage 5D CKD: Patients who have started dialysis

Cause of CKD: As decided by the treating physician

Hypocalcemia: Corrected Tca<8.5mg/dl

Hypercalcemia: Corrected TCa>10 mg/dl

Hypophosphatemia: Phosphorus <2.5 mg/dl

Hyperphosphatemia: Phosphorus>4.5mg/dl

Hypoparathyroidism:iPTH<15pg/ml

Hyperparathyroidism:iPTH>65 pg/ml

•**Data Management:**After the filled questionnaire is collected it will be checked for incompleteness manually by the investigator and Data was entered in SPSS ver 26.

•**Data Analysis:** Data was analyzed using SPSS ver 26 software. Descriptive statistics including means, standard deviation, and percentages wasused to describe the demographic and clinical data. Comparison between groups was performed using Chi-square and bivariate correlation coefficients. Multiple regression analysis was used to establish associations between clinical and biochemical findings. A 95% confidence interval was used for the determination of significance of probabilities i.e the difference will be significant when p value is< 0.05.

•**Ethical consideration:** The study is designed to see the prevalence and patterns of biochemical MBD abnormalities in selected consecutive CKD patients in TASH renal clinic and the collected data was anonymous. The participants didhave full right to withdraw from the study. The result of the study will lead to universal and routine CKD-MBD screening and treatment in patients with CKD on follow up if the finding is clinically significant and also will give light to further researches on the area. Ethical clearance was obtained from Addis Ababa University, college of medicine, internal medicine department.

Results

Patients baseline characteristics

A total of 100 patients were included in this study. Table 1 shows the demographic and clinical characteristics of the study patients. The majority were males (73%), from Addis Ababa (86%) and in the age group of 50-64 (40%). Majority of the patients have diabetes (40%) and Hypertension (25%). The mean age was 54.9 with the range of 19 to 92.

Table 1 - Demographic and clinical characteristics (n=100)

		Frequency (no = %)
Sex	**Male**	**73**
	Female	27
Age	18-34	14
	35-49	17
	50-64	**40**
	65-79	27
	≥ 80	2
Address	**Addis Ababa**	**86**
	Oromia	11
	Amhara	3
MaritalStatus	Single	16
	Married	**74**
	Divorced	6
	Widowed	4
Occupation	Civil Servant	12
	Merchant	3
	Farmer	1
	Housewife	5
	Self Employed	18
	Daily Laborer	7
	Student	5
	Other (retired, no job)	**49**
Educational Status	Unable to read and write	11

	Able to read and write	13
	Primary education	23
	Secondary education	26
	College and above	**27**
Religion	**Orthodox Christian**	**78**
	Protestant Christian	8
	Muslim	14
Smoking	**Never**	**94**
	Former	5
	Current	1
Co morbidity	Family History of CKD	10
	Coronary Artery disease	8
	Heart failure	9
	Cerebrovascular disease	6
	PAD	3
Stage of CKD	3a	23
	3b	**29**
	4	26
	5	22
Cause of CKD	Hypertension	25
	Diabetes	**40**
	Chronic GN	6
	Polycystic Kidney disease	4
	Obstructive Uropathy	8
	Others[1]	17
BMI	Underweight	8
	Normal Weight	**42**
	Overweight	37
	Obese	13
Blood Pressure	**Normal BP**	**34**
	High Normal BP	11
	Grade 1 Hypertension	17
	Grade 2 Hypertension	8
	Grade 3 Hypertension	3
	Isolated systolic Hypertension	27

1. Includes Unknown causes, TDF Nephropathy, Lupus Nephritis, Chronic Pyelonephritis 2o Reflux nephropathy and Tuberous Sclerosis

Laboratory results

Table 2 and 3 shows laboratory results and the frequency of various of mineral metabolism disorders of the study patients. Among the studied patients 36% were Hypocalcemic, 31% were Hyperphosphatemic and 89% developed secondary Hyperparathyroidism. Hyperparathyroidism was the most common mineral bone abnormality that was detected in this study. As the severity of CKD increases and there was a gradual increase in the prevalence of Hypocalcemia (from 21.7% to 68.2%),Hyperphosphatemia (from 4.3% to 68.2%) and Hyperparathyroidism (from 91.3% to 100%).

Table 2. Laboratory Results

Parameter	**Mean±SD**	**Range**
Creatinine (mg/dl)	3±2.02	1.3 - 12.4
GFR (ml/min/1.73m²)	29.6±14.7	5.1 - 57.8
Albumin (g/dl)	4±0.56	1.22 - 4.91
Corrected total Calcium (mg/dl)	8.4±1.18	3.70 - 10.40
Phosphorous (mg/dl)	4.1±1.47	1.40 - 12.40
Total PTH (pg/ml)	321.3 (4.9x)	32.80 - 1931.00
	IQR = 273.80	

Table 3. Frequency of various of mineral metabolism disorders

Parameter		**Stage of CKD**					**P-value**
		3a (n=23)	3b (n=29)	4 (n=26)	5 (n=22)	Total	
Calcium	Hypocalcemia	5 (21.7%)	6 (20.7%)	10 (38.5%)	15 (68.2%)	**36(36.0%)**	0.01
	Normal	17 (73.9%)	21 (72.4%)	16(61.5%)	7(31.8%)	61(61.0%)	
	Hypercalcemia	1 (4.3%)	2(6.9%)	0	0	3 (3.0%)	
Phosphorus	Hypophosphatemia	0	1 (3.4%)	3 (11.5%)	0	4 (4.0%)	<0.001

	Normal	22 (95.7%)	21(72.4%)	15(57.7%)	7(31.8%)	65(65.0%)	
	Hyperphosphatemia	1(4.3%)	7 (24.1%)	8 (30.8%)	15(68.2%)	**31(31.0%)**	
PTH	Normal	2(8.7%)	8(27.6%)	1(3.8%)	0	11(11.0%)	0.006
	Hyperparathyroidism	21(91.3%)	21(72.4%)	25(96.2%)	22(100.0%)	**89(89.0%)**	
	PTH ≥2x of ULN	13 (61.9%)	15 (71.4%)	23 (92%)	19 (86.3%)	**70 (78.6%)**	0.003
	PTH ≥9x of ULN	1 (4.3%)	2 (6.9%)	1 (3.8%)	7 (31.8%)	**11 (12.3%)**	

Correlation of serum PTH, calcium and phosphorus with patient characteristics

In the study using bivariate correlations patient's serum total calcium was found to have direct correlation with eGFR (r= 0.476, P <0.001) and age (r=0 .224, P=0.025)as well as inverse correlation with phosphorus (r= -0.5, P <0.001), PTH (r= -0.341, P = 0.001), diabetes as an etiology (r= -0.248, P=0.013), Urine dipstick (r= -0.158, P =0.048) and diastolic blood pressure (r= -0.246, P = 0.014). Additionally, serum Phosphorus was found to have direct correlation with PTH (r= 0.324, P=0.001), Urine dipstick (r= 0.161, P =0.044) and inverse correlation with GFR (r= -0.405, P<0.001), and Age (r= -0.229, P= 0.022). Whereas serum PTH was found to have direct correlation with diastolic blood pressure (r= 0.25, P = 0.012), Urine dipstick (r= 0.192, P =0.015), female sex (r= 0.391, P<0.001) and inverse correlation with GFR (r= -0.441, P<0.001), and Age (r= -0.4, P<0.001).

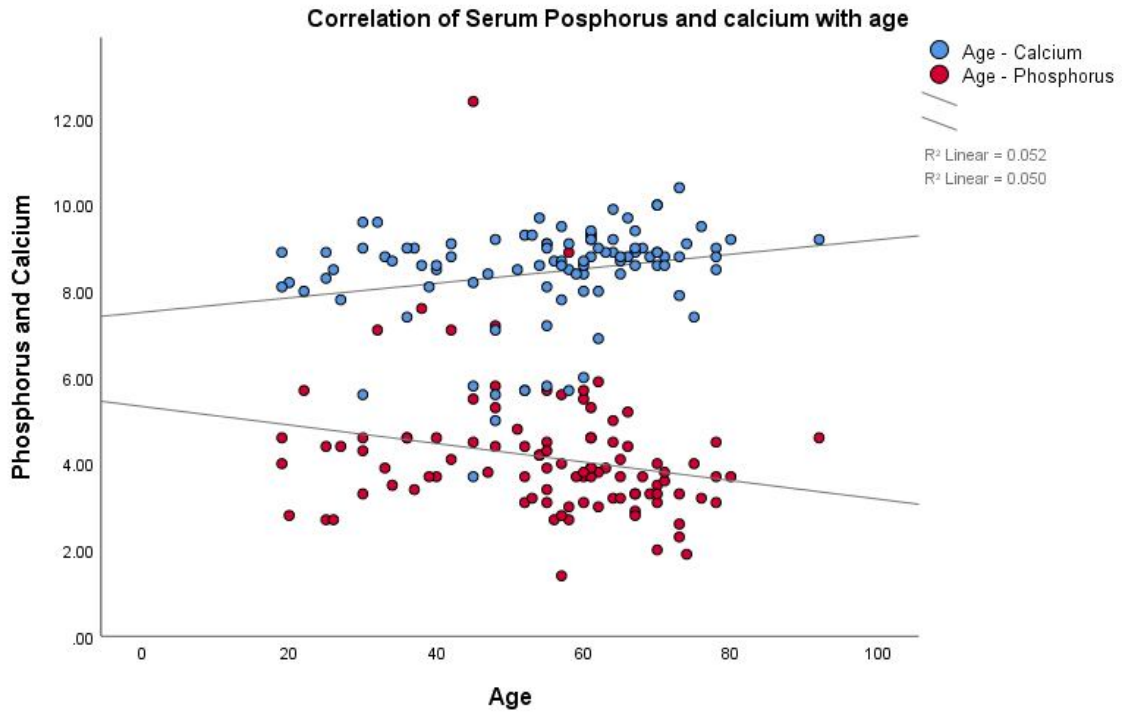

Figure1. Correlation of Serum Phosphorus and calcium with age in the study patients.

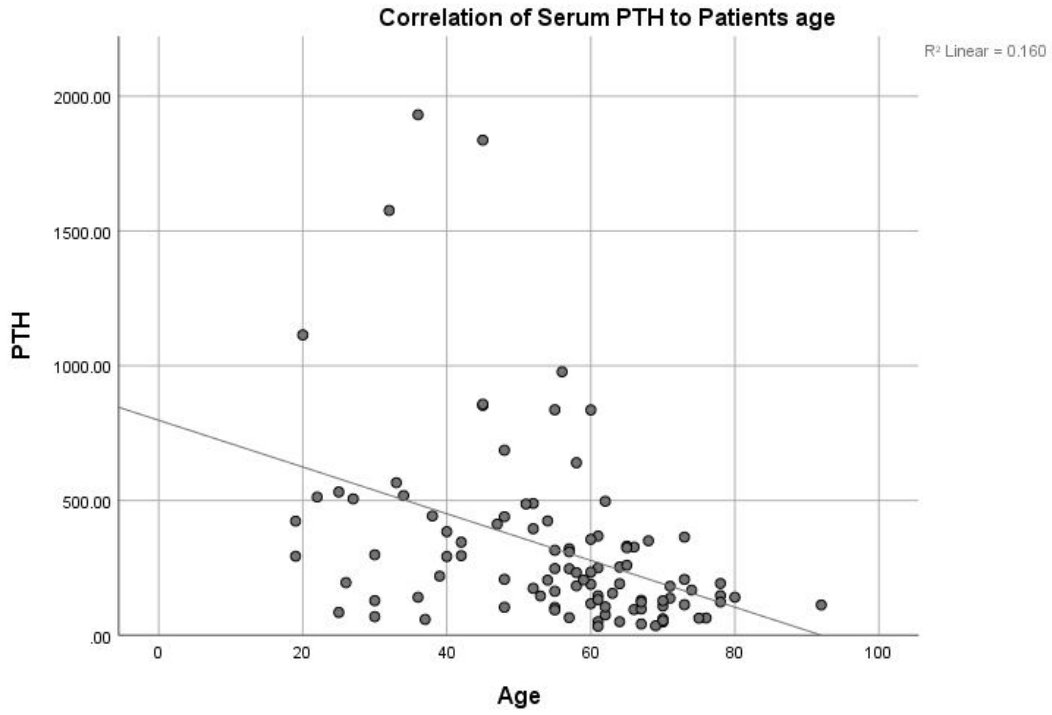

Figure 2. Correlation of Serum PTH with age in the study patients.

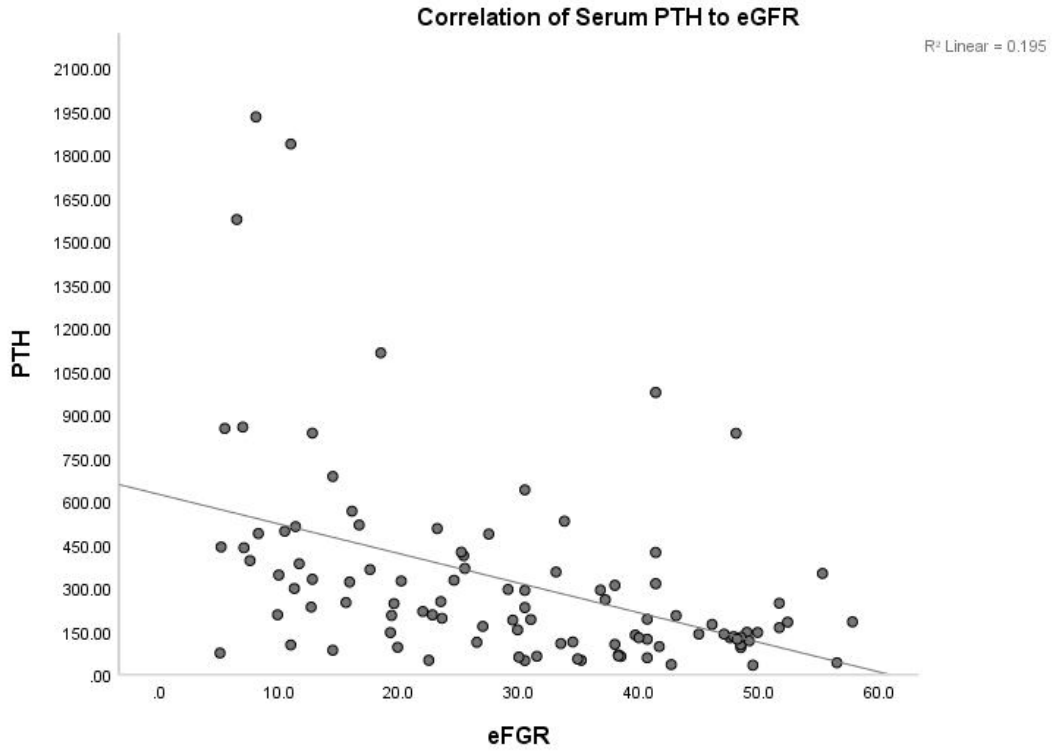

Figure 3. Correlation of Serum PTH with eGFR in the study patients.

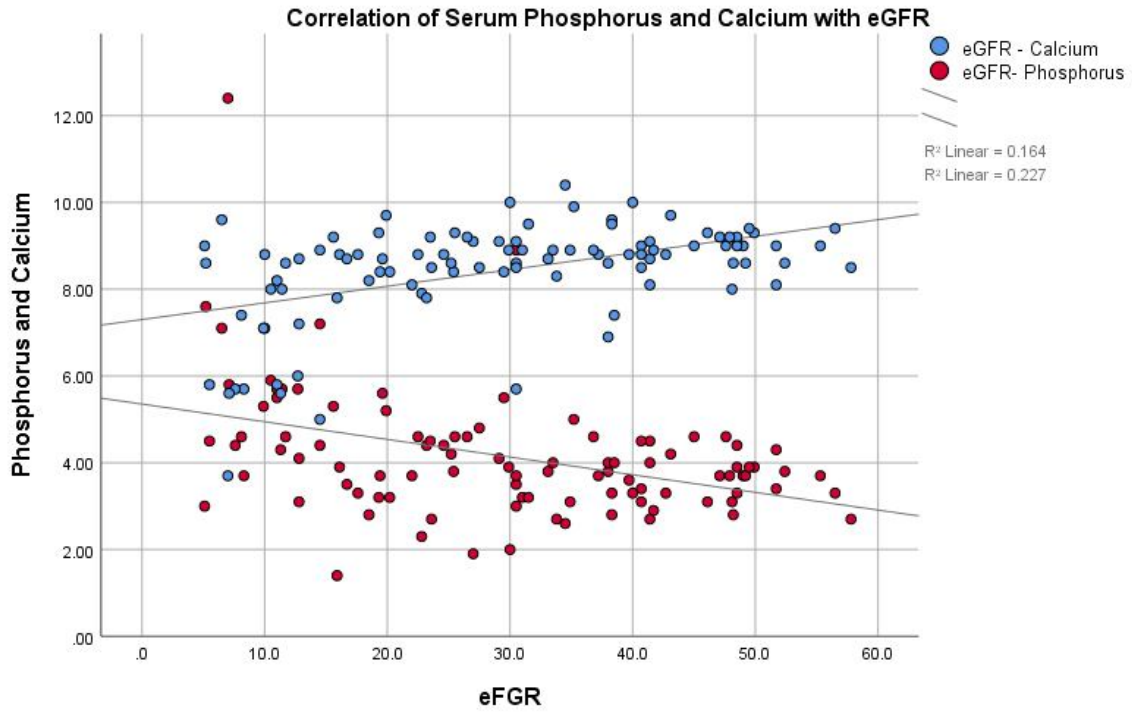

Figure 4. Correlation of Serum Phosphorus and calcium with GFR in the study patients.

However, on Multiple regression analysis, which explained 43.3% of calcium variation, the only independent predictors identified are GFR, diabetes, diastolic blood pressure and serum phosphorus (Table 4). Similarly, taking PTH as dependent variable, which explained 37.3% of PTH variation, diastolic blood pressure, female sex and eGFR were the only independent predictors identified (Table 5). But none of the above variables identified on bivariate correlation were independent predictors of phosphorus level on multiple regression analysis.

Table 4. Predictors of serum calcium in the studied CKD patients

Predictor	Beta	95%CI	P-value
Calcium	-	9.26 to 13.20	<0.0001
eGFR	0.349	0.01 to 0.04	0.001
Diabetes	-0.196	-0.87 to -0.07	0.022
DBP	-0.249	-0.04 to -0.01	0.004
Phosphorus	-0.275	-0.41 to -0.14	<0.0001

Table 5.Predictors of serum PTH in the studied CKD patients

Predictor	Beta	95%CI	P-value
PTH	-	-932.24 to 829.21	0.908
eGFR	-0.249	0.01 to 0.04	0.025
Female sex	0.264	-0.87 to -0.07	0.006
DBP	0.191	-0.04 to -0.01	0.036

Practice assessment on Management of CKD – MBD in Renal clinic of TASH

Among the 100 patient's that were included in this study in the past 6 months Urine protein was determined in 97%, calcium in 61%, Phosphorus in 62% and PTH in 15%. Abdominal U/S was documented in only 55% and urine dipstick for protein in 97% of the patients since the start of their follow-up (Table 6). Even though, treatment for CKD -MBD abnormalities was indicated for58% of Hyperphosphatemia, 58.3% of Hypocalcemia and 12.3% of Hyperparathyroidism patients only19.3%,20% and 5.6% respectively were startedon treatment (Table 7). The treatment they were on includes: 4 patients on both Alpha Calcidol and Calcium Carbonate, 9 patients only on Calcium Carbonate and 1 patient only on Alpha Calcidol. Assessment of

treatment target achievement for the specific abnormalities couldn't be done because of the small number of patients that were on treatment.

Table 6. Abdominal Ultrasound and urine dipstick finding

	Finding	**Frequency**
Abdominal Ultrasound (N=55)	Normal Kidney Size	21 (38.1%)
	Shrunken Kidney	21 (38.1%)
	Polycystic Kidney	4(0.7%)
	Hydronephrosis	6(0.12%)
	Others[1]	3(0.05%)
Urine Dipstick(N=97)	Negative	26 (26.8%)
	Trace to +1	12 (12.3%)
	+2 or more	59 (60.8%)
	Negative	26 (26.8%)

[1]Congenital renalanomaly

Table 7. Frequency of CKD patients that need MBD treatment and are on treatment

MBD abnormality	**Frequency**	**Needs Treatment**	**Frequency**	**On Treatment**
Hyperphosphatemia	31	Phosphorus >5mg/dl	18 (58%)	6 (19.3%)
Hypocalcemia	36	Calcium <8mg/dl	21 (58.3%)	8 (20%)
Hyperparathyroidism	89	PTH ≥9x ULN	11 (12.3%)	5 (5.6%)

Discussion

Disordered mineral metabolism i.e.,hypocalcemia, hyperphosphatemia and secondary hyperparathyroidism are common complications of CKD especially in those above stage 3.[5,17] A high prevalence of biochemical abnormalities of CKD‐MBD was found in this observational study involving CKD Stage 3–5 predialysis patients. These MBD abnormalities were 36% Hypocalcemia, 31% Hyperphosphatemia and 89% secondary Hyperparathyroidism.One study done on predialysis patients in south east Nigeria found70% hyperphosphatemia and 85% hyperparathyroidism which is similar with our finding of hyperparathyroidism.[11]Another study done in India in CKD patients stage 3-5D also showed hypocalcemia (23.8%), hyperphosphatemia (55.4%), secondary hyperparathyroidism (82.7%).[18]A similar high prevalence of disorders of mineral metabolism has been reported from the Western countries[17,19], India[18,20] and Nigeria[21,11].In addition, in our study the level of hypocalcemia, hyperphosphatemia and secondary hyperparathyroidism showed gradual increment with declining eGFR which was also demonstrated in other studies.[17,18]

Hyperparathyroidism was found in more than two thirds of the CKD patients, and its prevalence sharply increased with the decline in glomerular filtration, which is found in all of the patients with eGFR below 15 (stage 5). The results are similar to previous reports.[22] For example, in the Study for the Evaluation of Early Kidney Disease (SEEK), 90% of the subjects with eGFR <20mL/min/1.73m2 had high levels of iPTH and the prevalence in early stages of CKD (i.e., at eGFR >80mL/min/1,73m2 and between 60-70mL/min/1.73m2) was around 12% and 21%, respectively.[17] In our study we also found that female sex and high Diastolic blood pressure were independent predictors of hyperparathyroidism. Similar positive correlation with DBP was also found in a study done the south east Nigeria.[11]Furthermore, Blood Pressure Reduction After Parathyroidectomy and medical treatment with calcimmetics for Secondary Hyperparathyroidism was demonstrated in other studies.[23,24]The mechanism for this correlation was ascribed to alterations of calcium homeostasis and direct hypertensive activities induced by PTH.[25]In addition, in one study done on uremic patients also found that female patients have higher PTH level (approximately 69.6± 32.9 pg/ml) than males.[26,20]The effect of gender on parathyroid activity may be regulated by sex steroids, since estrogen receptors are present in parathyroid cells and estrogens increase PTH mRNA levels.[27,22]

Hypocalcemia was found in almost one third of the CKD patients and its prevalence also increased with decline in eGFR. This relation was also demonstrated in other studies. [19,18]We found diabetes to be an independent predictor of lower levels of calcium this could be due to higher number of patients (40%) that were diabetic in our study. No significant correlation was identified in serum calcium when diabetics were compared to non-diabetic CKD patients in study done in India. [18] The correlation between hyperphosphatemia and hypocalcemia was also demonstrated in other studies.[21]The inverse correlation between calcium and DBP was demonstrated in some studies.[28,29] In one study done on patients with essential hypertension showedthat Individuals with high diastolic blood pressure had significantly lower total serum calcium (2.41 ± 0.10 vs. 2.47± 0.10 mmol/1, mean± SD; P<0.01).[29] The effect was attributed to widespread depression of Ca(2+)-ATPase activity with plasma Ca2+ depletion and cytosolic Ca2+ overload, which may reflect an underlying membrane abnormality in essential hypertension.[30]

Hyperphosphatemia was also found in almost one third of the CKD patients and serum phosphate level also increased as the stage of CKD increased with 68% in stage 5. This was demonstrated in a Romanian study which showed that 93% of patients with high serum phosphate had a glomerular filtration rate below 30mL/min/1.73m2. [19]Even though the level of hyperphosphatemia increased with stage of CKD this wasn't demonstrated when multiple regression analysis was done.

In our assessment of the practice in the management of CKD MBD in renal clinic of TASH it was found that the screening for the biochemical abnormalities was low especially for serum PTH level and this has led to small number of patients to start treatment among the large number of patients that actually need it. The level of documentation of abdominal ultrasound to look for the causes of CKD was also low.

Conclusion

To conclude, this study found a spectrum of CKD‐MBD in CKD Stage 3–5. It showed that secondary hyperparathyroidism, hyperphosphatemia, hypocalcemia, were quite common in Ethiopian CKD patients. The most common type of MBD was hyperparathyroidism. The level of MBD abnormalities also worsen with progressive renal failure. Monitoring for CKD‐MBD should begin earlier on and treatment initiated accordingly.

Limitation of this study

Due to the cross-sectional nature of this study, patients were assessed only at presentation. Serum ALP, FGF-23 and 25(OH) D level weren't determined. The number of patients included were small because of the COVID pandemic limiting CKD patient from visiting follow-up clinics, research time constraint and couldn't get enough funding to do the laboratory investigations.

Recommendations

The level of screening for MBD biochemical abnormalities in CKD patients should increase especially in those above stage 3 in TASH renal clinic and once diagnosed treatment should be initiated. Further research on CKD MBD abnormalities is encouraged to be done at a national level.

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Annex

Declaration

I, the undersigned, declare that this postgraduate thesis is my original work, has not been presented for a degree in this or any other university and that all sources of material used for the thesis have been duly acknowledged.

Postgraduate Candidate: Sirak Melkeneh (MD, Internal Medicine Resident)

Signature: …….

Date of Submission: January 8, 2020

This thesis has been submitted with my approval and advisor.

Advisor: Addisu Melkie (MD, Internist, Nephrologist)

Signature: …….

Date: …….

Place: Addis Ababa, Ethiopia

Questionnaire

Date:

Addis Ababa University

College of health sciences

Faculty of Medicine

Department of Internal Medicine

Annex 1: QUESTIONNAIRE (For Patient interview)

This is a questionnaire prepared to undergo a study on the magnitude and patterns of biochemical MBD abnormalities among predialysis patients with CKD in TASH renal clinic. You will be asked a series of questions about your chronic kidney disease and other aspects associated with your health. We would like to assure you that none of the information obtained here will be used for any other purpose except for this study. You can refuse if you want not to be included in the study either at the start or at any time during the interview. We highly appreciate your contribution.

Date: _____ MRN/ICARE NUMBER: _____ Study ID: _____

1. Socio demographic characteristics

1.1. Age: _____

1.2. Sex: A) Male B) Female

1.3. Address: A) Addis Ababa b) Oromia C) Amhara D) SNPPR E) others (specify)

1.4. Marital status: A) Single B) Married C) Divorced D) Widowed

1.5. Occupation: A) Civil servant B) Merchant C) Farmer D) Housewife E) self-employed

F) Daily laborer G) student H) others (retired, no job) specify

1.6. Educational status: A) unable to read and write B) Able to read and write C) primary education D) secondary education E) college and above

1.7. Religion: A) Orthodox Christian B) Catholic Christian C) Protestant Christian D) Muslim

2. Clinical profile of CKD patient

2.1. Smoking status: A) Never B) former C) Current D) unknown

2.2. How often do you drink alcohol? A) Never B) former C) Current D) unknown

2.3. Do you have a sibling, parent or offspring who has chronic kidney disease?

A) Yes B) No

CHECKLIST(FOR CHART REVIEW)

2.5. Co morbidities (other than cause of CKD): A) Yes B) No

A) Coronary Artery Disease (CAD)

B) Heart Failure

C) Cerebrovascular disease

D) Peripheral arterial disease

E) Others (specify) _____

2.6. Any medication prescribed for treatment of co morbidity

A) No B) Yes (specify what medication was prescribed)

2.6. Stage of CKD: A) stage G1 B) stage G2 C) stage G3a D) stage G3b E) stage G4 F) stage G5

2.7. Presumed etiology of CKD

A). Hypertension B) Diabetes C) Chronic glomerulonephritis D) HIV E) polycystic kidney disease F) obstructive uropathy G) Unknown H) others (specify)

2.8. Most recent vital sign

1) BMI (kg/m^2): _____

2) Blood Pressure: Systolic blood pressure: _____ Diastolic blood pressure: _____

3. Laboratory profile of CKD patient

3.1. Most recent Creatinine (in mg/dl): _____

3.2. eGFR (ml/min/1.73m^2) using CKD-EPI (calculate both with and without race factor):

- With race factor _____ without race factor ----------

3.3. Urine protein on dipstick

A) Negative

B) Trace to +1

C) +2 or more

3.4. CKD Mineral bone disease panel

	available	Not available	Type of test
Serum calcium			a. Total calcium with albumin b. Total calcium without calcium c. Ionized calcium
Serum phosphorus			
PTH			A. Total PTH B. Intact PTH

3.5. Number of CKD-MBD panel determined and value of each CKD-MBD panel determined in the past 6month

CKD-MBD panel	Number determined	Value in the past 6month		
Serum calcium				
Serum phosphorus				
PTH				

3.6. HIV serology: A) reactive B) non-reactive C) unknown

4. Management of CKD-MBD

The following should be filled for those patients with diagnosis of CKD-MBD

4.1. was the patient started on treatment for CKD-MBD: A) Yes B) No

4.2. If the answer to above question is yes, what type of treatment was started?

Types of treatment	Tick the types of treatment given
Calcium carbonate	
Alpha calcidol	
Calcium carbonate and alpha calcidol	
Others (specify)	

4.3. Was target of treatment achieved: A) Yes B) No

4.4. Current CKD-MBD panel value

CKD-MBD panel	CKD-MBD panel current value
Serum calcium	
Serum phosphorus	
PTH	

Consent form

RESEARCH PROJECT PARTICIPATION CONSENT FORM: FOR PATIENTS

Information to study participants (Patients)

Title of the study project: **The Magnitude and patterns of biochemical MBD abnormalities among predialysis patients with CKD in TASH renal clinic, Addis Ababa, Ethiopia.**

Principal Investigator: Dr Sirak Melkeneh (MD, Internal medicine resident)

Procedure of the study: The study primarily involves data collection with interview using semi structured questionnaire and review of medical records of patients attending follow up clinic at TikurAnbessa Specialized Hospital (TASH) renal clinic.

Benefits, Risk or possible discomfort

Benefit: There is no direct benefit patients get as a result of being involved in the study. The participants will not be provided any payment and/or other incentives to take part in the study.

Risks: There is no risk associated with the study. No procedures will be done on patients during this study except for Blood pressure, Pulse, weight and height measurement.

Confidentiality and right to withdraw

Participants' information will be stored in a locked file to be only accessible for the purpose of the study only. The file will be organized and coded so that patients' specific identifiers will not be revealed at any point during the study.

Patients have the full right of refusing to withdraw at any point during the study.

Dear Participant,

My name is_____. I am one of the members of the group who are conducting this study. I am conducting a research project titled: Magnitude and patterns of biochemical MBD abnormalities among predialysis patients with CKD in TASH renal clinic, Addis Ababa, Ethiopia. Accordingly, I am grateful to inform you that you are selected to be a participant of the study. By participating in the study, you will provide us about 30 minutes of your time in answering certain questions related to your disease.

All the information you provide us will be kept confidential. There is no risk associated with the study to you. You have full right to decline involvement in the study or withdraw from the study at any point during the interview. Finally, we kindly ask you to give as a genuine response.

Once you decide to involve in the study please put your signature in the space provided below to describe that you willingly decided to participate in the study.

Signature of participant: _____ Date: _____

Signature of the interviewer: _____ Date: _____

Contact information

This research project will only be carried out after approval from the Ethical review committee of department of internal medicine and of Addis Ababa University. If you have any questions and concerns you can contact Dr. Sirak Melkeneh by any of the following addresses

Dr. Sirak Melkeneh

Mob: 0910934495

Email: sirak.melkeneh@aau.edu.et

ለጥናቱ ተሳታፊዎች የመረጃ ቅጽ

በአዲስ አበባ የኒቨርሲቲ ጤና ሳይንስ ኮሌጅ በድህረ ምረቃ ትምህርት ፕሮግራም የውስጥ ደዌ ትምህርት ክፍል፡፡

ከዚህ በታች እንደ ተመለከተዉ በአዲስ አበባ የኒቨርሲቲ በድህረ ምረቃ ትምህርት ፕሮግራም የውስጥ ደዌ ትምህርት ክፍል የኩላሊት ሕመምተኞችን በሚመለት አነስተኛ ጥናት በጥቁር አንበሳ ሆስፒታል የኩላሊት ክፍል እያካሄድን ነዉ፡፡

የዚህ ጥናት ተሳታፊ ለመሆን እርስዎተ ጋብዘዋል፡፡ በጥናቱ ላይ ከመሳተፎ በፊት ጥናቱን በተመለከተ አስፈላጊ የሆኑ መረጃዎችን ማግኘት ያስፈልግዎታል፡፡ ስለሆነም በጥናቱ ላይ ለመሳተፍም ሆነ ላለመሳተፍ መጀመሪያ ማወቅ የምገባዎትን መረጃ እንደምከተለዉ እናቀርብልዎታለን፡፡

1. **የጥናቱ አላማ፡** ስር በሰደደ የኩላሊት ሕመምተኞት ላይ በተጓዳኝ ሊመጡ ከሚችሉ ችግሮች ውስጥ የደም ማነስና የሰውነት ንጥረ ነገሮች መጠን መዛባትን ለማሳወቅ ነው፡፡
2. **በጥናቱ የሚካተቱ ተሳታፊዎች፡** ማንኛዉም ከስድስት ወር በላይ ስር በሰደደ የኩላሊት ሕመም ክትትል የሚያደርግ ግለሰብ እና ደረጃውም ሦስተኛና ከዚያ በላይ የሆነ ለክትትል የመጣ/ች እና ለመረጃዉ ፍቃደኛ የሆነ/ች፡፡
3. **በጥናቱ የሚካሄዱ ነገሮች፡-** ጥናቱ የሚካሄደዉ ለዚህ ጥናት የተዘጋጀውን ቃለ መጠይቅ ማድረግ፣ አካላዊ ምርመራ እና የደም ናሙና መውሰድ ናቸው፡፡
4. **ከጥናቱ ጋር የተያያዘ ጉዳት፡ ጥናቱ በተሳታፊዎች**/ሕመምተኞች አካል ላይም ሆነ አእምሮ ላይ ፈፅሞ የሚያደርሰው ጉዳት የለም፤የሚያደርሰው ነገር ቢኖር የእርስዎን ግዜ መሻማትና የደም ናሙና ሲወሰድ የሚሰማ ሕመም ብቻ ነው፤ ያልገባዎትን መረጃ ለመመለስ አይገደዱም፡፡
5. **ጥቅም፡** በጥናቱ በመሳተፍዎ የሚከፈልዎት ክፍያ ወይም የተለየ ጥቅም የለዉም፡፡ በሌላ በኩል በጥናቱ ላይ በመሳተፍዎ ለሚጠየቁት ጥያቀዎች ተገቢዉን መረጃ መስጠትዎና የደም ናሙና ውጤትዎ ስር በሰደደ የኩላሊት ሕመምተኞች ክትትል አገልግሎት ላይ ከፍተኛ እገዛ ይኖረዋል፡፡
6. **ሚስጥር የመጠበቅ ሁኔታ፡** በጥናቱ ላይ የእርስዎ ስምና ካርድ ቁጥር አይጠቀስም፤ የሚሰጡት መረጃም በሚስጥር ይጠበቃል፤ ለሶስተኛ ሰዉ ተላልፎአ ይሰጥም፡፡

ማንኛውም የጥናቱ ተሳታፊ በማንኛውም ሰዓት ጥናቱን የማቋረጥ መብት አለው፡፡

<u>የጥናት አድራጊው መግለጫ</u>

እኔ ስሜ ----------የምባለው በጥናት አድራጊው ቡድን ውስጥ አንዱ አባል ነኝ፡፡

ይህ ጥናት ስር በሰደደ የኩላሊት ሕመምተኞት ላይ በተጓዳኝ ሊመጡ ሚችሉ ችግሮች ውስጥ የደም ማነስና የሰውነት ንጥረ ነገሮች መጠን መዛባትን ለማሳየት ነዉ፡፡

በጥናቱ ላይ መሳተፍዎ ሙሉ በሙሉ የሚመሰረተዉ በራስዎ ፍላጎትና ፍቃደኝነት ላይ ነዉ፡፡ ከመጀመሪያዉ በጥናቱ ላይ መሳተፍም ሆነ ላለመሳተፍ ይችላሉ፡፡ ያልገባዎትን መረጃ ለመመለስ አይገደዱም፡፡ ስምዎት ከመረጃዉ ጋር አይካታትም፡ የሰጡት መረጃ ሁሉ በሚስጥር እነደሚጠበቅልዎቃል እንገባለን፡፡

ጥናቱ የሚወስደዉ ግዜ በአማካይ 30 ደቂቃ ብቻ ነዉ፡፡ ይህ ጊዜዎትን የሚይዝ ቢሆንም በጥናቱ ላይ በመሳተፍዎ ለሚጠየቁት ጥያቀዎች ተገቢዉን መረጃ መስጠትዎና የደም ናሙና ውጤትዎ ስር በሰደደ የኩላሊት ሕመምተኞች ክትትል አገልግሎት ለይ ከፍተኛ ሚናያለዉ በመሆኑ እንድተባበሩን እንጠይቅዎታለን፡፡

የተወሰኑ ደቂቃዎች ባነጋግርዎ ፈቃደኛነዎት፤ በመጨረሻም ስላዳመጡኝ ከልብ አመሰግናለሁ፡፡

የጥናት አድራጊው ፊርማ ---------- ቀን፡ ----------

<u>የጥናት አድራጊዎች አድራሻ፡</u>

1. ዶ/ርሲራክመልኬነህ፡-

የሞባይልስ/ቁ0910934495፣ኢሜይል<u>sirak.melkeneh@aau.edu.et</u>

አዲስ አበባ የኒቨርሲቲ

ጤና ሳይንስ ኮለጅ

በሕክምና ትምህርት

የውስጥ ደዌ ትምህርት ክፍል (8ኛ ፎቅ)

የጥናቱ ተሳታፊ ፈቃደኝነት ማረጋገጫ

እኔ ስሜ ----------የምባለው ስለ ጥናቱ ዓላማ፣ጉዳትና ጥቅም በጥናት አድራጊው ቡድን በተረዳሁት መሠረት በጥናቱ ለመሳተፍ ፈቃደኛመሆኔን በፊርማዬ አረጋግጣለሁ፡፡

የተሳታፊው ፊርማ ---------- ቀን፡ ----------

Thank You for your Participation