Original Article

Status Of Vitamin D, Parathyroid Hormone And Carotid Artery Intima Media Thickness And Its Correlation With Estimated Glomerular Filtration Rate In Patients With Chronic Kidney Disease

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Abstract

Chronic kidney disease the most common feature is hypovitaminosis D leading to secondary hyperparathyroidism. This would have caused an increase in calcium and a decrease in phosphate levels. Arterial wall thickness can be measured by carotid intima media thickness test. Early detection of these changes may hint the need for a more aggressive approach towards heart disease and stroke. Ethical committee approval was obtained by Institutional Ethical committee. The study consists of 60 CKD patients divided into 3 groups based on eGFR and 20 normal healthy individuals, age and sex matched individuals between the age group of 30-60 years. Informed consent was taken from the patients and controls. Demographic data was collected followed by history regarding current health status, history of medication, alcoholism and Active smoking. Serum creatinine was estimated by alkaline picrate method, blood urea was estimated by Urease method, serum calcium level was estimated by OCPC method and serum phosphorous was estimated by Ammonium Molybdate method. Serum 25 OH vitamin D and serum will be analyzed by ELISA method. Serum PTH was estimated by ELISA method. Carotid artery ultrasound scans will be recorded for each participant with a 10-MHz linear-array transducer to measure intima media thickness. This study helpful to label an early alarming marker to prevent the worst progression of CKD by estimating Vitamin D, PTH and CIMT. The progression and complications of CKD, especially the cardiovascular complications can be prevented or at least postponed to some extent.

Keywords: Chronic kidney disease, Vitamin D, parathyroid hormone, carotid intima media thickness, estimated GFR

INTRODUCTION

Chronic Kidney Disease (CKD) is characterized by irreversible sclerosis and loss of nephrons. The renal mass progressively declines over a prolonged period, depending on the underlying etiology [1]. CKD patients are classified five stages based on Glomerular Filtration Rate (GFR). Diabetes and hypertension could stand as the main etiology for the increased incidence of CKD. It affects 10-16% of the adult population worldwide [2]. In India, the recent estimate is found to be 229 per million population [3]. The National Kidney Foundation (NKF) Task Force on Cardio vascular Disease in CKD demonstrated the prevalence of cardio vascular disease in CKD and associated high death rate [4].

Vitamin D is well known factor that regulates bone and mineral metabolism by promoting calcium, phosphate absorption and suppressing Parathyroid hormone (PTH) secretion [5]. It is renoprotective with suppression of the renin–angiotensin–aldosterone system, and with anti proteinuric as well as anti-inflammatory effects [6]. It has antiatherosclerotic role that includes inhibition of macrophage to foam cell formation, down regulation of vascular smooth muscle cell proliferation and migration and suppression of inflammation triggered expression of endothelial adhesion molecules. Besides, vitamin D also prevents vascular calcification by inhibition of bone morphogenic protein-2 expression. Decreased vitamin D can cause low calcium and hyperparathyroidism. PTH normally causes absorption of calcium and excretion of phosphorous [7].

In CKD the most common feature is hypovitaminosis D leading to secondary hyperparathyroidism. This would have caused an increase in calcium and a decrease in phosphate levels. But due to the declined renal mass, this does not happened PTH secretions further stimulated [8]. These may alter the vascular smooth muscle cell proliferation and reprogram the osteoblastic changes, finally leading to increase arterial wall thickness [9].
Arterial wall thickness can be measured by carotid intima media thickness test (CIMT) and the extent of carotid

atherosclerotic vascular disease may be estimated. The test measures the thickness of the inner two layers of the carotidartery, the intima and the media. Early detection of these changes may hint the need for a more aggressive approach towards heart disease and stroke [10].

Though CKD can have a deleterious consequence of CVD and increased mortality, estimation of Vitamin D, PTH, Calicum, Phosphorous and Measuring CIMT might throw a warning sign of the future risk. Early intervention could help the CKD patients for a better life and outcome. The aim of present study is evaluate the status of Vitamin D, Parathyroid hormone and Carotid artery Intima Media Thickness and its Correlation with estimated Glomerular Filtration Rate in patients with Chronic Kidney Disease.

MATERIALANDMETHODS

Type of study
Case - Control study.

Study Population
Study population was patients and attendants who attend the Department of Nephrology.

Sample size
80 in which 20 will be normal healthy individuals and 60 will be CKD patients with stage 3to5.

Selection Criteria
Inclusion Criteria
The patients attending Nephrology Department diagnosed with CKD.

Exclusion Criteria
Known Subjects with history of smoking, alcoholism and medicines which influence serum calcium and vitamin D levels was excluded. Patients with any debilitating illness also excluded from the study.

Study design
Ethical committee approval was obtained by Institutional Ethical committee. The study consists of 60 CKD patients divided into3groupsbasedoneGFRand20normalhealthyindividuals, age and sex matched individuals between the age group of30-60years.Informed consent was taken from the patients and controls. Demographic data was collected followed by history regarding current health status, history of medication, alcoholism and Active smoking.

Sample collection
About 5 ml of venous blood was collected from all the subjects for the study for biochemical analysis.

Sample Analysis
Serum creatinine was estimated by alkaline picrate method [11], blood urea was estimated by Urease method [12], serum calcium level was estimated by OCPC method [13] and serum phosphorous was estimated by Ammonium Molybdate method [14]. Serum 25 OH vitamin D and serum will be analyzed by ELISA method [15]. Serum PTH was estimated by ELISA method [16].

Estimated GFR (eGFR)
Estimated GFR will be computed by employing Mayo Clinic Quadratic Equation (MCQE) based on serum creatinine and age in years [17].
The MCQE estimated GFR (ml/min/1.73m2)
=exp [1.911+5.249/SCr–2.114/SCr2–(0.00686 x age (years)](–0.205 if female)

Carotid artery intima media thickness Test
Carotid artery ultrasound scans will be recorded for each participant with a 10-MHz linear-array transducer to measure intima media thickness (IMT) in the far wall of the right and left common carotid arteries within 2 cm proximal to the carotid bulb. The region with the thickest IMT, excluding areas with focal lesions, will be measured. The average IMT will be calculated from the right and left IMT measurements .All focal plaques within the carotid tree (common, internal, and external carotid arteries and bulb) will be identified as wall thickness. The area of each plaque will be calculated as the average lesion thickness (in mm) multiplied by the lesion length (in mm).In those participants with multiple plaques, plaque area will be the sum of the areas of all plaques observed in the carotid tree [18].

Statistical analysis
Data will be expressed in Mean and Standard deviation (mean ±SD). Unpaired student's t-test will be used for comparison of means between controls and cases. The statistical significance will be determined at 5% ($p < 0.05$) level. Comparison of means across the groups will be done by ANOVA. Vitamin D, Parathyroid hormone and CIMT will be correlated with eGFR by Spearmen correlation.

RESULTS

Table1: Demographic data between Control and Cases

Parameter	Control(n=20)	CKD Stage 3(n=20)	CKD Stage 4(n=20)	CKD Stage 5(n=20)
Age(years) Mean±SD	50.95±8.30	48.85±9.64	50.45±7.49	52.30±6.86
Sex: Male/female	15/5	**15/5**	12/8	14/6

The above table shows age and sex matched individuals were considered for the study.

Table2: Blood urea, creatinine and eGFR between Control and Cases

Parameter	Control(n=20)	CKD Stage 3(n=20)	CKD Stage 4(n=20)	CKD Stage 5(n=20)	ANOVA
Blood Urea (mg/dL) Mean ±SD	19.75±4.20	52.25±11.19	81.15±24.56	116.45±16.80	F=131.129 p<0.0001
Serum Creatinine (mg/dL)Mean±SD	0.92±0.13	2.01±0.13	3.07±0.31	6.01±0.42	F=1251.18 p<0.0001
eGFR (mL/min)Mean±SD	126.68±14.45	39.54±4.27	20.01±3.83	9.85±1.14	F=932.420p<0.0001

The above table shows the mean blood urea and serum creatinine were significantly higher in CKD patients when compared with control. The mean serum eGFR was significant lower in CKD patients when compared with Control.

Table3: Serum Calcium and Phosphorus level between Control and Cases

Parameter	Control(n=20)	CKD Stage 3(n=20)	CKD Stage 4(n=20)	CKD Stage 5(n=20)	ANOVA
Serum Calcium(mg/dL) Mean±SD	10.17±0.65	8.78±0.42	8.59±0.22	7.98±1.90	F=16.087p<0.0001
Serum Phosphorus(mg/dL) Mean±SD	3.66±0.27	4.38±0.35	4.97±0.56	5.65±0.35	F=90.979p<0.0001

The above table shows the mean serum calcium was significantly lower in CKD patients when compared with control. The mean serum PTH was significant higher in CKD patients when compared with Control.

Table4: Serum Vitamin D and PTH level between Control and Cases

Parameter	Control (n=20)	CKD Stage 3(n=20)	CKD Stage 4(n=20)	CKD Stage 5(n=20)	ANOVA
Serum VitaminD(ng/mL) Mean±SD	42.50±4.45	30.90±4.33	24.95±2.98	21.45±3.45	F=115.067p<0.0001
Serum PTH(pg/mL) Mean±SD	39.75±3.04	82.10±10.56	103.90±12.45	212.60±36.32	F=272.147p<0.0001

The above table shows the mean serum Vitamin D was significantly lower in CKD patients when compared with control. The mean Serum PTH was significant higher in CKD patients when compared with Control.

Table5: CIMT level between Control and Cases

Parameter	Control(n=20)	CKD Stage 3(n=20)	CKD Stage 4(n=20)	CKD Stage 5(n=20)	ANOVA
CIMT Left side(mm) Mean±SD	0.50±0.06	0.72±0.05	0.82±0.05	0.85±0.04	F=196.797 p<0.0001
CIMT Right side(mm) Mean±SD	0.49±0.05	0.71±0.05	0.80±0.05	0.86±0.04	F=231.209 p<0.0001
Mean CIMT(mm) Mean±SD	0.50±0.06	0.72±0.05	0.81±0.05	0.86±0.04	F=198.889 p<0.0001

The above table shows the Carotid Intima Media Thickness (CIMT) both Left and Right side were significant higher in CKD patients when compared with Control. The mean CIMT was significantly higher in CKD patients compared with control. The increase is statistically significant (p<0.0001).

Table6: Correlation of Vitamin D, PTH and CIMT with eGFR

Parameter	Control(n=20)	CKD Stage 3(n=20)	CKD Stage 4(n=20)	CKD Stage 5(n=20)
Vitamin D	r=-0.30727 (p =0.0975)	r= 0.05396 (p=0.4107)	r=-0.01983 (p=0.4669)	r= 0.54034 (p=0.0045)
PTH	r=0.00303 (p=0.4949)	r= 0.1074 (p=0.3261)	r=0.37625 (p=0.0510)	r=-0.88412 (p<0.0001)
CIMT	r=0.19358 (p=0.2067)	r=-0.27108 (p=0.1239)	r=-0.56712 (p=0.0045)	r=-0.80244 (p<0.0001)

The above tables shows Vitamin D, PTH and CIMT were not correlated to eGFR in control, CKD stage 3 and. In CKD stage 4 Vitamin D and PTH were not correlated to eGFR whereas CIMT was negatively correlated with eGFR and it is statistically significant. In CKD stage 5Vitamin D was positively correlated with eGFR and it is statistically significant. (p<0.001).PTH and CIMT were negatively correlated with eGFR and itis statistically significant.(p<0.001).

DISCUSSION

In the present study vitamin D , PTH and carotid artery intima media thickness in Chronic Kidney Disease have been assayed along with its Correlation with estimated Glomerular Filtaration Rate. The diagnosis of Chronic Kidney Disease was made on the basis of history, physical examination, routine investigation, specific biochemical investigations and ultrasonographic findings.

In present study, 80 subjects were taken up for study to determine the vitamin D , PTH and carotid artery intima media thickness and divided in to control and CKD cases. Controls group consists of 20 subjects and CKD cases are further divided in CKD Stage 3, CKD Stage 4 and CKD Stage 5 each CKD stage contains 20 subjects each. Investigations were carried out in each case to assess their biochemical parameters and relevant information were gathered and tabulated.

In the present study it has been observed that mean age of control was 50.95, In CKD Stage3 it was 48.85, In CKD Stage 4 it was 50.45 and CKD Stage 5 it was 52.30. It has been observed that most of subjects are male, in control group 15 were male and 5 were female. In CKD Stage 3 group 15 were male and 5 were female, In CKD Stage 4 group 12 were male 8 were female and CKD Stage 5group14 were male and 6were female.

In the present study the mean blood urea in CKD Stage 3, CKD Stage 4 and CKD Stage 5 were52.25, 81.15 and 116.45 respectively and these are higher than that of control (19.75). This increase is statistically significant (p<0.0001). In the present study the mean Serum Creatinine in CKD Stage3, CKD Stage4 and CKD Stage5 were 2.01, 3.07 and 6.01 respectively and these are higher than that of control(0.92). This increase is statistically significant (p<0.0001). The increased blood urea and serum creatinine in CKD patients is due to decline in glomerular filtration.

In the present study the mean estimated GFR in CKD Stage 3, CKD Stage 4 and CKD Stage 5 were 39.54, 20.01 and 9.85 respectively and these are lower than that of control (126.68). This decrease is statistically significant (p<0.0001). Renal impairment exact status cannot provide by serum creatinine alone. Appreciable increase of serum creatinine required 50% fall in GFR. Estimated GFR based serum creatinine will provide more accurate results. Increased serum creatinine and decreased eGFR was identified in CKD in this present study it was similar to the findings of Chijioke et. al, [19], Increased mean serum creatinine shows late presentation of CKD cases in this study it was same findings of Ifeoma et al, It is because most of the CKD patients were under conservatively therapy than renal replacement therapy (RRT) [20].

In the present study the mean serum calcium in CKD Stage 3, CKD Stage 4 and CKD Stage 5 were 8.78, 8.59 and 7.98 respectively and these are lower than that of control (10.17). This decrease is statistically significant (p<0.0001). In the present study the mean Serum Phosphorus in CKD Stage3,CKD Stage4 and CKD Stage5 were 4.38, 4.97 and 5.65 respectively and these are higher than that of control (3.66).This increase is statistically significant (p<0.0001).

In the present study the mean serum Vitamin D in CKD Stage 3, CKD Stage 4 and CKD Stage 5 were 30.90, 24.95 and 21.45 respectively and these are lower than that of control (42.50). This decrease is statistically significant (p<0.0001). In the present study the mean Serum PTH inCKDStage3, CKD Stage4 and CKD Stage5 were 82.10, 103.90 and 212.60 respectively and these are higher than that of control (39.75). This increase is statistically significant (p<0.0001). Declined kidney function leads to decreased vitamin D synthesis. Vitamin D inhibit cyclin-dependent kinase-2 activity and further causes suppression vascular smooth muscle cell proliferation [21]. In CKD decreased vitamin D associated with increased CIMT value. In this study mean serum calcium and Vitamin D were lowered in CKD patients than controls. Whereas serum phosphate and parathyroid hormone level were increased in CKD patients than in control.

In the present study the mean CIMT left side in CKD Stage 3, CKD Stage 4 and CKD Stage 5 were 0.72, 0.82 and 0.85 respectively and these are higher than that of control (0.50). This increase is statistically significant (p<0.0001). The mean CIMT right side in CKD Stage 3, CKD Stage 4 and CKD Stage 5 were 0.71, 0.80 and 0.86 respectively and these are higher than that of control (0.49). This increase is statistically significant (p<0.0001).The mean CIMT in CKD Stage3,

CKD Stage4 and CKD Stage5 were0.72, 0.81 and 0.86 respectively and these are higher than that of control (0.50). This increase is statistically significant ($p<0.0001$). LuXia Zhang et. al, study reported that in CKD stage 2 and 3 CIMT was significantly raised and concluded the progression CKD will causes arterial change. [22] Preston et. al, shown that Stage 3 and 4 have raised CIMT compared with Normotensive.[23] Atherosclerotic changes in carotid arteries might be indicative of atherosclerosis of coronary arteries. CIMT is a non-invasive marker for generalized atherosclerosis and good indicator for coronary heart disease.

In the present study correlation of Vitamin D, PTH and CIMT with eGFR was conducted. In control and CKD stage3 Vitamin D, PTH and CIMT were not correlated to eGFR and it is not statistically significant. In CKD stage 4 VitaminD ($r=-0.01983$) and PTH ($r=0.37625$) were not correlated to eGFR whereas CIMT ($r= -0.56712$) was negatively correlated with eGFR and it is statistically significant ($p<0.001$). In CKD stage 5 Vitamin D ($r= 0.54034$) was positively correlated with eGFR and it is statistically significant.($p<0.001$).PTH ($r=-0.88412$) and CIMT ($r= -0.80244$) were negatively correlated with eGFR and it is statistically significant.($p<0.001$)

The present study findings correlation of biochemical parameters in different stages of CKD is found similar to Rahman et. al., It has noted that decreased calcium, decreased vitamin D, increased phosphate and hyperparathyroidism are most important features of CKD [24]. This is similar to study of Malawadi et. al., it also shown increased serum phosphate and parathyroid and also shown decreased levels of serum calcium and eGFR compared to the control the study does not shown vitamin D Status [25].

In this present study regarding PTH and eGFR was comparable to the Rahman et. al., study they also correlated the parathyroid hormone with biochemical parameters in chronic kidney disease Ian H. de Boer et al, study shown increased PTH value as the advanced stage of CKD [26].Staloposky et al, study confirmed that increased PTH is a most common feature of CKD [27]. The high levels of mean PTH due to reduced serum calcium and continuous increase of serum phosphate from early to advanced renal failure. The handling of calcium by renal system differs in different stage of CKD. This type of trend is mostly identified from CKD stage 3onwards.

This study helpful to label an early alarming marker to prevent the worst progression of CKD by estimating Vitamin D, PTH and CIMT. The progression and complications of CKD, especially the cardiovascular complications can be prevented or at least postponed to some extent. Supplementation of vitamin D along with calcium would be more beneficial. A chelating phosphate molecule would be a challenge in the coming years to add to the benefits of the treatment for CKD. The quality of life can be improved for the CKD patients to a near normal condition.

Conflict of interest: No conflict of interest

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