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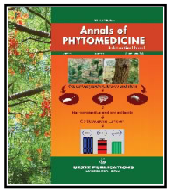

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Evaluation of biochemical profile based on vitamin D status and severity of disease in stage 3 to stage 5 chronic kidney disease

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Abstract

In chronic kidney disease major cause of mortality is cardiovascular disease. This mortality of cardiovascular is more in as disease advances. In CKD, there is decreased vitamin D and hyperphosphataemia and development of end-stage renal disease. Hence, aim of present study was asses the relationship between bone mineral parameters and atherogenic index of plasma based on vitamin D status. The study contains 45 control group and 135 will be CKD individuals with stage 3 to stage 5, each stage consists of 45 each. In all the subjects atherogenic index of plasma, blood urea, creatinine, serum calcium, serum phosphorus vitamin D and parathyroid hormone are estimated. The mean serum calcium and vitamin D were decreased in CKD whereas phosphorus, magnesium and parathyroid hormone (PTH) were increased compared with control and it is statistically significant. There was positive correlation glomerular filtration rate (GFR) with calcium, vitamin D. Whereas, GFR withatherogenic index of plasma (AIP), phosphorous, magnesium; PTH was shown negative correlation and it is statistically significant. There was no significance difference of GFR, AIP, phosphorus, magnesium and PTH between Group 1 (vitamin D deficiency) and Group 2 (vitamin D insufficient). Whereas, Group 1 Vs Group 3 (vitamin D sufficient) and Group2 vs. Group 3 shown a statistically significance difference. The assessment of these parameters will be helpful in prevent of future risk and also helpful in better life and outcome from cardiovascular risk in chronic kidney disease.

1. Introduction

In chronic kidney disease (CKD), there is a progressive decline of renal mass (Gooneratne *et al.*, 2008). CKD remains silent in early stages and end stage kidney disease (ESKD) is the finally stage. Chronic kidney disease, a major chronic disorder is increasing globally with prevalence of 13.4%. CKD affects 10-16% of the adult population in Europe, Australia, Asia and USA. In India, study done on 2013, it has been estimated prevalence was 17.4%. The risk factors for CKD are diabetes (Shavnam *et al.*, 2020) high blood pressure, glomerulonephritis, hyperlipidemia, obesity, smoking and decreased antioxidants also leads to kidney disease (Mounika and Hymavathi, 2021). Besides this, other causative risk factors for CKD are those having family history of CKD, Low birth weight, malnutrition CKD and also caused by different synthetic drugs (Punit *et al.*, 2019). In CKD, major cause of mortality is cardiovascular disease. This cardiovascular mortality is higher in dialysis patients, it is up to 500 times compared with age matched normal population (Brenner *et al.*, 1994).

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Vitamin D will obtained from two sources that is dietary source and produced in the skin. Besides animal sources plant source, will play major role in the vegans for the source of vitamin D and prevent vitamin D deficiency. The vegan food sources are mushroom, fortified plant based milk like soy milk and almond milk. The vitamin D is also obtained from fortified cereals and fortified orange juice. The green leafy vegetables like spinach contain small quantity of vitamin D. In thehumans, vitamin D precursor form is cholecalciferol, it undergo subsequent hydroxylation at position 25 and 1 yields calcitriol (Paramita *et al.*, 2021). Vitamin D stimulates calcium and phosphate absorption from intestine (Artaza *et al.*, 2009). The vitamin D, binds to the vitamin D receptor (VDR). Deficiency of vitamin D is a risk factor for the development of end stage kidney disease. Low vitamin D level in hemodialysis linked to endothelial dysfunction. Vitamin D decreases the activity of rennin system and act as renoprotective. It is also act as anti-inflammatory (Yuva *et al.*, 2020). Vitamin D also suppress the macrophages to formation of foam cell, declines the vascular smooth muscle cell proliferation and also causes the decreased activity of endothelial adhesion molecules. Calcium is a major element present in the body fluid (Ahmad and Ghosh, 2020). Calcium activity is regulated by calcitriol. Declined calcitriol leads decreased calcium and high parathyroid hormone. It will also lead to increased phosphate and increased magnesium level (Brewer *et al.*, 2011).

In CKD, different contributing factors such as tumor necrosis factor, cytokines and interferon, indoxylsulfate, hyperglycemia, dyslipidemia and oxidative stress decreases the kidney klotho, in turn reflects to blood level (Shimizu *et al.*, 2011). Declined klotho levels causes phosphate retention by lowering urinary phosphate excretion, it will stimulate fibroblast growth factor-23 (FGF23) synthesis. High blood FGF23 suppresses vitamin D synthesis and worsens vitamin D deficiency. Elevated phosphate causes re-programming of vascular smooth muscle cells in to chondrocytes and osteoblast. It also causes fibrogenesis of renal tissue and improper regeneration of kidney tissue and finally leads to chronic kidney disease chronic progression.

Atherogenic index of plasma (AIP) shows the association between atherogenic and protective lipoprotein. It is also related to dimension of pre atherogenic and antiatherogenic lipoprotein level (Nupur, 2021). CKD was strongly associated with dyslipidemia and causes increased risk of atherogenic index of plasma, which is strong indicator for cardiovascular disease. Vitamin D deficiency also induce cardiovascular risk. Hence, aim of present study was to assess the relationship between bone mineral parameters and atherogenic index of plasma based on vitamin D status. The objectives are estimation of atherogenic index of plasma, serum calcium, phosphorus, magnesium, vitamin D and parathyroid hormone level.

2. Materials and Methods

2.1 Study population

The study took place at Saveetha Medical College and hospital and the study was case control study. The sampling method is convenient sampling method. The study consists of 180 subjects in which normal healthy individuals are 45 and 135 are CKD patients which contain stage3 to stage 5, each stage contains 45 subjects.The patients included are diagnosed with chronic kidney disease individuals who are attending the Nephrology Department, Saveetha Medical College.

2.2.1 Inclusion criteria

Cases: Known diagnosed patients of chronic kidney disease attended the Department of Nephrology of Saveetha Medical College (Defined as reduced GFR less than 60 ml/min/1.73m^2 for > 3 months with an elevated blood urea and serum creatinine level).

Controls: Age and sex matched healthy individuals along with non-smoker and nonalcoholic were included as control.

Age group of 30-70 years for both cases and controls.

2.2.2 Exclusion criteria

Patients were excluded, if they have any of the following:

Patients with viral hepatitis and HIV positive.

Life threatening illness andhistory of malignancy.

Cerebrovascular disease

Systolic blood pressure > 200 mmHg and diastolic blood pressure > 160 mmHg.

Patient history of liver diseases.

Drugs which influences the vitamin D level.

Patients with age less than 30 and greater than 70 are excluded.

2.3 Ethical consent

Ethical clearance obtained from the Institutional Ethical Committee with a Reference Number: 002/06/2018/IEC/SMCH. All procedures performed in the study were conducted in accordance with ethical guidelines. All participants were given Informed consent.

2.4 Demographic parameters

Demographic data such as age, gender, smoking and alcoholic status were recorded. All the participants detailed clinical history was noted. In all the subjects, body mass index (BMI) was calculated by using weight in kg divided by height in meters squared.

2.5 Biochemical investigations

Routine biochemical parameters were estimated by standard fully automatic chemistry analyzer. From the control and patient subjects, fasting serum triglycerides, HDL-cholesterol, blood urea, serum creatinine, serum calcium, serum phosphorus and magnesium are estimated. Serum 25(OH) vitamin D level was determined by enzyme-linked immunosorbent assay (My Bio Source) normal range is 30-100 ng/ml. As per national kidney foundation (NKF), kidney disease outcome quality Initiative (NKF/KDOQI) guidelines vitamin D less than 5 ng/ml consider as severe deficiency, vitamin D between 5-15 ng/ml consider as deficiency and vitamin D between 16-30 ng/ml is consider as vitamin D insufficiency (Kandula *et al.*, 2011). Serum parathyroid hormone (PTH) level was estimated by a enzyme-linked immunosorbent assay (My Bio Source) normal range is 10-65 pg/ml. Based on serum creatinine using modified diet renal disease formula, glomerular filtration rate estimated. eGFR=186 x (Serum Creatinine (mg/dl))$^{-1.154}$ x (age in years)$^{-0.203}$ x 0.742 in case of female multiply with 0.742 (Levey *et al.*, 1999). Based on the formula, CKD patients are divided in to CKD stage 3 with eGFR = 30-59 ml/ min per 1.73 m^2, CKD stage 4 with eGFR 15-29 ml/min per 1.73 m^2 and CKD stage 5 with eGFR less than 15 ml/min per 1.73 m^2. Atherogenic index of plasma calculation done by using log (Triglycerides/HDL-C) formula. Based on the AIP value, cardiovascular risk will be assessed AIP lower than 0.11 consider low risk, If AIP among 0.11 to 0.21 consider as intermediate risk and AIP greater than 0.21 as consider high risk (Dobiasova and Frohlich, 2006).

2.6 Statistical analysis

The statistical analysis was done using SPPS 16.0 for Windows (SPSS Inc., Chicago, IL, USA). Statistically expressed as mean ± SD.

Comparison of parametric values across the Groups were done by ANOVA, whereas nonparametric values such as smoking alcoholic and disease state across the groups were done by chi-square test. Correlation done by pearson correlation. The multiple comparisons by using post hoc with least significant difference test was done for biochemical parameters in various groups of vitamin D status. Significance is considered if, *p* value is less than 0.05.

3. Results

In this study, total 180 subjects were taken in which control was 45 and chronic kidney disease patients were 135. Estimated GFR was calculated by using MDRD formula. Estimated GFR chronic kidney disease individuals are further classified in to stage 3 CKD, stage 4 CKD and stage 5 CKD, each stage consists of 45 patients each.

Table 1: Characteristics data in control and different stages of CKD

Parameter	Control (n=45)	Stage 3 of CKD (n=45)	Stage 4 of CKD (n=45)	Stage 5 of CKD (n=45)	Significance
Age	45.6 ± 9.9	47.7 ± 11.4	45.2 ± 7.7	47.0 ± 9.7	>0.05
Sex : Male : Female	27:18	25:20	24:21	23:22	>0.05
BMI (kg/m^2)	21.8 ± 2.0	21.0 ± 2.1	21.6 ± 2.3	20.9 ± 2.5	>0.05
Smokers (%) Yes: No	(0%) 0:45	(15.5%) 7:38	(22.2%) 10:35	(20%) 9:36	<0.05
Alcoholic (%) Yes: No	(0%) 0:45	(20%) 9:36	(20%) 9:36	(20%) 9:36	<0.05
Systolic blood pressure (mm/Hg)	118.6 ± 9.3	140.2 ± 21.5	149.2 ± 16.6	146.2 ± 15.6	<0.0001
Diastolic blood pressure (mm/Hg)	77.8 ± 5.5	85.6 ± 9.2	86.0 ± 9.4	86.7 ± 7.1	<0.0001
Etiology: Diabetesmellitus (%)	0 (0%)	24 (53.3%)	21 (46.7)%	19 (35.6%)	<0.05
Glomerulonephritis (%)	**0 (0%)**	**5 (11.1%)**	**7 (15.6%)**	**5 (11.1%)**	**<0.05**
Hypertension (%)	**0 (0%)**	**13 (28.9%)**	**15 (33.3%)**	**20 (44.4%)**	**<0.05**
Polycystic kidney disease (%)	**0 (0%)**	**3 (6.7%)**	**2 (4.4%)**	**1 (2.2%)**	**<0.05**

p<0.05 consider as significant.

There is no significance difference in age, sex and BMI between control and all stage of CKD. Smokers and alcoholic are not present in control group, whereas in CKD stage 3 to CKD stage 5, minimum numbers were registered as smokers and alcoholics. Systolic blood pressure and diastolic blood pressure are significantly raised in CKD stages than compared with control (Table 1).

Table 2: Blood urea, creatinine, eGFR, between control and different stages of CKD

Parameter	Control (n=45)	Stage 3 of CKD (n=45)	Stage 4of CKD (n=45)	Stage 5 of CKD (n=45)	Significance
Blood urea(mg/dl) Mean ± SD	27.31 ± 6.44	45.57 ± 11.31	65.0 ± 11.94	81.20 ± 14.35	F=190.09 *p*<0.0001
Creatinine (mg/dl) Mean ± SD	0.83 ± 0.07	1.83 ± 0.25	3.01 ± 0.44	5.38 ± 0.66	F=965.49 *p*<0.0001
eGFR (ml/min) Mean ± SD	95.58 ± 10.80	38.06 ± 7.40	21.62 ± 4.25	10.74 ± 2.36	F=1313.86 *p*<0.0001

F = distribution

Blood urea and serum creatinine are significantly elevated in CKD stage 3 to stage 5, when compared with control. In present study estimated GFR by MDRD shown decline in CKD stages than compared with control. This decrease is statistically significant (Table 2; *p* <0.0001).

Table 3: Atherogenic index incontrolanddifferent stages of CKD

Parameter	Control (n=45)	Stage 3 of CKD (n=45)	Stage 4 of CKD (n=45)	Stage 5 of CKD (n=45)	Significance
Atherogenic index of plasma					
Mean ± SD	0.07 ± 0.040	0.17 ± 0.075	0.27 ± 0.133	0.33 ± 0.160	F=46.56; p<0.0001

The mean atherogenic index was significant higher in CKD stages when compared with control. The increase is statistically significant (Table 3; p<0.0001).

Table 4: Bone minerals level in control and different stages of CKD

Parameter	Control (n=45)	Stage 3 of CKD (n=45)	Stage 4 of CKD (n=45)	Stage 5 of CKD (n=45)	ANOVA
Serum calcium (mg/dl) Mean ± SD	9.7 ± 0.63	8.7 ± 0.35	8.3 ± 0.32	7.9 ± 0.50	F=110.773; p<0.0001
Serum phosphorus (mg/dl) Mean ± SD	3.8 ± 0.34	4.3 ± 0.33	5.1 ± 0.49	5.9 ± 0.40	F=248.388; p<0.0001
Calcium X phosphorus: Mean ± SD	36.9 ± 3.5	37.2 ± 2.9	43.0 ± 4.4	47.4 ± 0.34	F=88.131; p<0.0001
Serum magnesium (mg/dl) Mean ± SD	1.8 ± 0.24	2.2 ± 0.31	3.5 ± 0.58	3.7 ± 0.58	F=195.668; p<0.0001
Serum vitamin D (ng/ml) Mean ± SD	33.8 ± 10.3	26.3 ± 6.6	21.6 ± 5.9	18.7 ± 4.3	F=38.74; p<0.0001
Serum PTH (pg/ml) Mean ± SD	45.3 ± 10.4	83.8 ± 11.2	107.2 ± 10.7	340.5 ± 120.9	F=213.96; p<0.0001

The serum calcium decreased in different stages CKD patients when compared with control and it is statistically significant (p<0.0001). The mean phosphorus, Ca X P and magnesium are increased in different stages when compared with control and it is statistically significant (p<0.0001). The mean serum vitamin D was significantly lower in different stages CKD patients when compared with control. The mean serum PTH was significant higher in different stage CKD patients when compared with control and it is statistically significant (Table 4).

Table 5: Correlation of bone minerals, vitamin D and PTH with eGFR

	r value	p value
Atherogenic index of plasma (AIP)	**-0.6680**	<0.0001
Calcium	**0.782**	<0.0001
Phosphorus	**-0.773**	<0.0001
Magnesium	**-0.748**	<0.0001
Vitamin D	**0.640**	<0.0001
PTH	**-0.604**	<0.0001

The correlation between GFR and calcium, vitamin D was positive and it is statistically significant. The correlation coefficient between GFR and AIP, phosphorous, magnesium, PTH was negative and it is statistically significant (Table 5).

Based on vitamin D level in CKD, they are again classified as Group 1 where vitamin D is between 5-15 ng/ml, consider as deficiency and Group 2 where vitamin D between 16-30 ng/ml is consider as vitamin D insufficiency. Group 3 where vitamin D between 31-100 ng/ml is considered as vitamin D sufficiency. The GFR was registered lower in vitamin D deficiency group than vitamin D sufficient. The atherogenic index of plasma was higher in vitamin D deficiency group and it is statistically significant. The calcium and vitamin D are significantly lower in vitamin D deficiency group than compared with other groups. There was a statistically significant increased level of phosphorous, magnesium, and PTH in vitamin D deficiency group (Table 6).

Table 6: Various parameters based on the vitamin D status in CKD

Parameter	Group 1 vitamin D deficiency n=9	Group 2 vitamin D insufficient n = 105	Group 3 vitamin D sufficient n = 21	ANOVA
eGFR(ml/min) Mean ± SD	18.2 ± 10.1	21.6 ± 11.2	36.6 ± 12.0	F=16.564; p<0.0001
Atherogenic index of plasma Mean ± SD	0.39 ± 0.13	0.27 ± 0.13	0.13 ± 0.07	F=14.612; p<0.0001
Calcium (mg/dl) Mean ± SD	7.8 ± 0.50	8.3 ± 0.45	8.8 ± 0.36	F=17.111; p<0.0001
Phosphorus (mg/dl) Mean ± SD	5.6 ± 0.76	5.2 ± 0.78	4.6 ± 0.65	F=7.481; p<0.005
Calcium × Phosphorus: Mean ± SD	43.5 ± 4.6	42.9 ± 5.7	40.0 ± 5.1	F=2.528 NS
Magnesium (mg/dl) Mean ± SD	3.7 ± 0.55	3.2 ± 0.80	2.2 ± 0.54	F=18.973; p<0.0001
Vitamin D (ng/ml) Mean ± SD	12.1 ± 2.5	21.0 ± 3.9	33.5 ± 1.6	F=153.410; p<0.0001
PTH (pg/ml) Mean ± SD	284.6 ± 174.6	181.9 ± 133.8	87.4 ± 26.2	F=8.576; p<0.0001

NS-Not Significant

Table 7: Post hoc analysis of various parameters based on the vitamin D status in CKD

Parameter	Group 1 Vs. Group 2 (Mean difference, Std. error)	Group 2 Vs. Group 3 (Mean difference, Std. error)	Group 3 Vs. Group 3 (Mean difference, Std. error)
eGFR(ml/min)	(3.43, 3.92) NS (>0.05)	(18.42, 4.48)<0.0001	(14.99, 2.70)<0.0001
Atherogenic index of plasma (AIP)	(0.12, 0.44) NS (>0.05)	(0.25, 0.51)<0.0001	(0.13, 0.03)<0.0001
Calcium (mg/dl)	(0.55, 0.15) <0.0001	(0.99, 0.17)<0.0001	(0.43, 0.10)<0.0001
Phosphorus (mg/dl)	(0.45, 0.26) NS (>0.05)	(1.04, 0.30)<0.005	(0.59, 0.18)<0.005
Calcium X Phosphorus	(0.60, 1.92) NS (>0.05)	(3.48, 2.20) NS (>0.05)	(2.88, 1.33) NS (>0.05)
Magnesium (mg/dl)	(0.45, 0.26) NS (>0.05)	(1.47, 0.29)<0.0001	(1.02, 0.18)<0.0001
Vitamin D (ng/ml)	(9.09, 1.21)<0.0001	(21.4, 1.38)<0.0001	(12.3, 0.83)<0.0001
PTH (pg/ml)	(102.64, 44.0) NS (>0.05)	(197.19, 50.33)<0.0001	(94.55, 30.37)<0.005

The multiple comparisons by using post hoc with least significant difference test between groups based on vitamin D status. Post hoc analysis shown that there was no significance difference of eGFR, AIP, phosphorus, magnesium and PTH between Group 1 and Group 2. Whereas, Group 1 Vs Group 3 and similarly Group 2 Vs. Group 3 shown a statistically significance difference of eGFR, AIP, phosphorus, magnesium and PTH. But, calcium × phosphorus not showed any significant difference between any two groups (Table 7).

4. Discussion

In this study, most of the CKD stages 3 to stage 5 individual primary disease state is diabetes mellitus, followed by hypertension, glomerulonephritis and poly cystic kidney disease. Diabetic leads to different complication in this diabetic nephropathy is the one of the major complication (Sanjeev and Divya, 2021). The blood urea and serum creatinine are increases gradually from stage 3 of CKD to stage 5 of CKD due to decreased GFR. In chronic kidney disease, there is an abnormal disturbance in lipid metabolism that is decreased HDL and increased triglycerides (Smita *et al.*, 2020). It will leads to raised atherogenic index of plasma. From stage 3 to stage 5, there is continuously raise of atherogenic index value. The decreased triglycerides will leads to antihyperlipidemic activity (Rashmi *et al.*, 2019) and prevent atherogenicity.

As chronic kidney disease progress, there will be increased phosphate and decreased vitamin D and declined action of

parathyroid hormone on bone, which causes decreased serum calcium level. Calcium is major regulator molecule for parathyroid hormone secretion. Calciums act on parathyroid gland chief cells through membrane receptor (Llach *et al.*,1995). As chronic kidney disease advances, there will be declined vitamin D level and resistance action of PTH on bone. There is inverse relationship between calcium and PTH secretion. In CKD decreased level of calcium receptors leads insufficient inhibition of PTH secretion. It leads high parathyroid hormone level (Martin and Gonzales, 2007). As chronic kidney disease advances, there is decline of GFR and there is a decrease of calcium and vitamin D. Whereas, AIP, phosphorous, magnesium, PTH are increased along with decreased GFR. As vitamin D deficiency increasing beside the stage of disease, there is altered biochemical parameters were noticed. It is strong evidence that as severity of chronic kidney disease increases, the vitamin D deficiency also increases, leading to raised value of atherogenic index of plasma. It is evident that vitamin D deficiency will cause atherogenic action.

The fibroblast growth factor inhibits phosphate reabsorption and calcitriol synthesis inhibition by inhibiting 1 alpha hydroxylase activity. The vitamin D level enhances parathyroid hormone directly or indirectly (Andress *et al.*, 2008). The parathyroid hormone indirectly declines intestinal absorption of calcium, It will further leads to hypocalcaemia which will leads to stimulation of parathyroid hormone. Raise of phosphaturic hormone fibroblast growth factor will causes low vitamin D. Klotho is a transmembrane protein it is strongly expressed in the distal convoluted tubules (DCT) and proximal convoluted tubule (Hruska et al., 2008). Klotho required for fibroblast growth factor-23 (FGF-23) binding. The bone cells, mainly osteoblast is responsible for secretion and synthesis of FGF-23. FGF23 causes decreased phosphate concentration and declines vitamin D level (Urakawa *et al.*, 2006).

Chronic kidney disease progress from stage 3 to stage 5, there will be phosphate retention due to decline filtration, which will be main causative factor for secondary hyperparathyroidism (Slatopolsky *et al.*, 1996). Decreased calcium, increased phosphate and decreased vitamin D activity will causes increased parathyroid hormone gene expression. As GFR decreased below the 30 ml/min, there will be declined level of vitamin D. It also registered in previous studies, if there is mild to moderate chronic kidney disease, there will be declined vitamin D. Various other studies also noticed that uremic toxin will inhibits vitamin D synthesis (Tentori *et al.*, 2008) . The principal disturbances in CKD are excess PTH, vitamin D deficiency, and phosphate retention. Altered PTH and vitamin D levels causes CKD progression, secondary hyperparathyroidism, left ventricular hypertrophy and cardiovascular mortality (Burnett *et al.*, 2006).

5. Conclusion

This study is helpful to understand the status of calcitriolinchronic kidney disease and deficiency of vitamin D will leads to abnormal changes in bone minerals and increased atherogenic index of plasma. The estimating these parameters act as early indicators for diagnosis of worst progression of CKD. It will also helpful to identify the cardiovascular complications. By early estimating these parameters can be prevented or at leastpostponed to some extent of worst prognosis. Supplementation of vitamin D can be improved for the CKD patients to a near normal condition and it can improve the quality of life.

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Conflict of interest

The authors declare no conflicts of interest relevant to this article.

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