**International Journal of Medical and Pharmaceutical Research**

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

# Status of serum TNF-a, vitamin D, and carotid artery intima–media thickness and their association across different stages of chronic kidney disease

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*Received: 07-01-2026*
*Accepted: 15-01-2026*
*Published: 15-02-2026*



## ABSTRACT

Tumor Necrotic Factor-α (TNF-α) is a potent pro inflammatory cytokine produced by glomerular mesangial cells and tubular epithelial cells. It causes deposition of fibrin in the glomeruli, vasoconstriction and cellular infiltration, it will lead to reduced glomerular filtration rate. In CKD the most common feature is hypovitaminosis D leading to secondary hyperparathyroidism. Carotid Intima Media Thickness (CIMT) is used to measure the extent of carotid arterial wall thickness associated with cardiovascular risk factors and with cardiovascular outcomes. Ethical committee approval was obtained by Institutional Ethical committee. Informed consent was taken from all the patients. Demographic data is collected, followed by history regarding current health status, history of medication, alcoholism and active smoking was taken. The study consists of 90 CKD patients divided into 3 groups based on their staging of CKD. Group 1 was patients of stage 1, 2; In Group2 patients of stage 3, 4 were included; Group3 contains patients of end stage renal disease (ESRD) stage 5. We observed that Calcium, Vitamin D decreased in CKD Groups, whereas, serum Phosphate, PTH and Serum TNF-α levels showed an increase. In Group II and Group III Serum TNF-α was negatively correlated and in Group III vitamin D positively correlated with eGFR. CKD is due to profound inflammatory changes with hypocalcaemia, hyperphosphataemia, hypovitaminosis D, and secondary hyperparathyroidism.

***Keywords:*** Chronic kidney disease, Vitamin D, parathyroid Tumor Necrotic Factor-α, carotid intima media thickness, estimated GFR.

## INTRODUCTION

Chronic Kidney Disease (CKD) is characterized by irreversible sclerosis and loss of nephrons [1]. It affects 10-16% of the adult population worldwide [2]. In India, the recent estimate is found to be 229 per million populations [3]. The National Kidney Foundation (NKF) Task Force on Cardiovascular Disease in CKD demonstrated the prevalence of cardiovascular disease in CKD and associated high death rate [4]. People with high blood pressure, diabetics and people with a family history of kidney failure are at the highest risk of developing CKD.

Persistent, systemic or intra renal micro inflammation is a hallmark feature of CKD, being involved in progressive decrease of renal mass over a period of time .There are many factors that contribute to chronic inflammatory status in CKD, including increased production of pro inflammatory cytokines, oxidative stress and acidosis, chronic and recurrent infections, altered

metabolism of adipose tissue, and intestinal dysbiosis. These inflammation-mediated alterations can induce irreversible tubular injury and nephron failure leading to decreased filtration and [5]. CKD is classified in to five stages based on the estimated glomerular filtration rate (eGFR).

Tumor Necrotic Factor-$\alpha$ (TNF-$\alpha$) is a potent pro inflammatory cytokine produced by glomerular mesangial cells and tubular epithelial cells. It causes deposition of fibrin in the glomeruli, vasoconstriction and cellular infiltration, it will leads to reduced glomerular filtration rate (GFR). It induces a respiratory burst in macrophages and stimulates the release of free radicals and thus, promotes renal scaring [6].

Vitamin D is well known factor that regulates bone and mineral metabolism by promoting calcium, phosphate absorption and suppressing Parathyroid hormone (PTH) secretion [7]. It is renoprotective with suppression of the renin–angiotensin–aldosterone system, and with antiproteinuric as well as anti-inflammatory effects [8]. 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 [9].

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 happen and PTH secretion is further stimulated [10]. These may alter the vascular smooth muscle cell proliferation and reprogram osteoblastic changes, finally leading to increased arterial wall thickness [11].

Carotid Intima Media Thickness (CIMT) is used to measure the extent of carotid arterial wall thickness associated with cardiovascular risk factors and with cardiovascular outcomes. The CIMT estimates carotid artery inner two layer thickness, the intima and the media. Initial measurement of these modifications may alarm the need for a more careful approach towards stroke and heart disease [12].

Though CKD can have a deleterious consequence of CVD and increased mortality, estimation of TNF-$\alpha$, Vitamin D, PTH, Calcium, 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.

## METHODOLOGY

### Type of study

Randomized prospective study.

### Study Population

Study population was patients with different stages (stage 1 to stage 5) attend the Department of Nephrology.

### Sample size

90 patients with different stages of CKD was included in the study. They are further divided in to three groups.
Group 1: Patients of stage 1, 2.
Group2: Patients of stage 3, 4.
Group3: Patients of end stage renal disease (ESRD) stage 5.

### Selection Criteria

### Inclusion Criteria

The patients attended 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. Informed consent was taken from all the patients. Demographic data is collected, followed by history regarding current health status, history of medication, alcoholism and active smoking was taken. The study consists of 90 CKD patients divided into 3 groups based on their staging of CKD. Group 1 was patients of stage 1, 2; In Group2 patients of stage 3, 4 were included; Group3 contains patients of end stage renal disease (ESRD) stage 5.

### 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 [13], blood urea was estimated by Urease method [14], serum calcium level was estimated by OCPC method [15] and serum phosphorous was estimated by Ammonium Molybdate method [16]. Serum 25 OH vitamin D and PTH, serum TNF-$\alpha$ were analysed on Seimens ADVIA Centaur by Chemi Luminiscent Immuno Assay (CLIA) method. Estimated GFR (eGFR) was computed by employing Mayo Clinic Quadratic Equation (MCQE) based on serum creatinine and age in years [17].

**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). The statistical significance will be determined at 5% ($p < 0.05$) level. Comparison of means across the groups will be done by ANOVA. Serum TNF-$\alpha$ and Vitamin D levels was correlated with eGFR in different groups of CKDS.

## RESULTS

**Table 1: Demographic data between different CKD Groups**

| Parameter | Group I (n=30) | Group II (n=30) | Group III (n=30) |
|---|---|---|---|
| **Age (years) Mean ± SD** | 47.30±9.91 | 49.46±8.02 | 51.63±6.52 |
| **Sex : Male/female** | **19/11** | 18/12 | 19/11 |

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

**Table 2: Blood urea, creatinine and eGFR between different CKD Groups**

| Parameter | Group I (n=30) | Group II (n=30) | Group III (n=30) | ANOVA |
|---|---|---|---|---|
| **Blood Urea (mg/dL) Mean ± SD** | 40.76±11.36 | 66.96±21.36 | 115.23±18.13 | F=140.51 p<0.0001 |
| **Serum Creatinine (mg/dL)Mean ± SD** | 1.30±0.18 | 2.65±0.68 | 6.14±0.39 | F=867.86 p<0.0001 |
| **eGFR (mL/min) Mean ± SD** | 77.18±7.15 | 28.67±11.54 | 9.65±1.07 | F=588.49 p<0.0001 |

The above table shows the mean blood urea and serum creatinine were significantly higher in Group II and Group III patients when compared with Group I. The mean serum eGFR was significant lower in Group II and Group III patients when compared with Group I.

**Table 3: Serum Calcium and Phosphorus level between different CKD Groups**

| Parameter | Group I (n=30) | Group II (n=30) | Group III (n=30) | ANOVA |
|---|---|---|---|---|
| **Serum Calcium (mg/dL) Mean ± SD** | 8.70±0.43 | 8.57±0.21 | 7.78±0.86 | F=23.03 p<0.0001 |
| **Serum Phosphorus (mg/dL) Mean ± SD** | 4.43±0.32 | 4.96±0.53 | 5.58±0.37 | F=57.31 p<0.0001 |

The above table shows the mean serum calcium was significantly lower in Group II and Group III patients when compared with Group I. The mean serum Phosphorus was significant higher in Group II and Group III patients when compared with Group I.

**Table 4: Serum Vitamin D and PTH level between different CKD Groups**

| Parameter | Group I (n=30) | Group II (n=30) | Group III (n=30) | ANOVA |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| **Serum Vitamin D (ng/mL) Mean ± SD** | 30.90±3.95 | 24.70±3.26 | 21.10±3.03 | F=62.45 p<0.0001 |
| **Serum PTH (pg/mL) Mean ± SD** | 83.06±11.12 | 104.93±13.83 | 219.87±37.98 | F=276.60 p<0.0001 |

The above table shows the mean serum Vitamin D was significantly lower in CKD Group II and Group III patients when compared with Group I. The mean Serum PTH was significant higher in CKD Group II and Group III patients when compared with Group I.

**Table 5: Serum TNF-*α* level between different CKD Groups**

| **Parameter** | **Group I (n=30)** | **Group II (n=30)** | **Group III (n=30)** | **ANOVA** |
|---|---|---|---|---|
| **Serum TNF-*α* (pg/mL) Mean ± SD** | 17.03±2.37 | 30.60±4.65 | 48.13±5.99 | F=346.64 p<0.0001 |

The mean Serum TNF-*α* was significant higher in CKD Group II and Group III patients when compared with Group I.

**Table 6: CIMT level between different CKD Groups**

| **Parameter** | **Group I (n=30)** | **Group II (n=30)** | **Group III (n=30)** | **ANOVA** |
|---|---|---|---|---|
| **CIMT Left side (mm) Mean ± SD** | 0.73±0.05 | 0.82±0.05 | 0.84±0.04 | F=46.81 p<0.0001 |
| **CIMT Right side (mm) Mean ± SD** | 0.71±0.05 | 0.81±0.05 | 0.85±0.04 | F=82.10 p<0.0001 |
| **Mean CIMT (mm) Mean ± SD** | 0.72±0.05 | 0.82±0.05 | 0.85±0.04 | F=73.15 p<0.0001 |

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

**Table 7: Correlation of TNF-*α* and Vitamin D with eGFR in different CKD Groups**

| **Parameter** | **Group I (n=30)** | **Group II (n=30)** | **Group III (n=30)** |
|---|---|---|---|
| **TNF-*α*** | r= 0.04007 (p=0.8334) | r= -0.59629 (p=0.00051) | r= -0.84697 (p<0.0001) |
| **Vitamin D** | r= 0.33186 (p=0.0732) | r= 0.10323 (p=0.58722) | r= 0.94626 (p=<0.0001) |

The above tables shows TNF-*α* and Vitamin D were not correlated to eGFR in Group I, In Group II TNF-*α* and Vitamin D were not correlated to eGFR whereas CIMT was negatively correlated with eGFR and it is statistically significant. In Group III TNF-*α* was negatively correlated with eGFR and it is statistically significant. (p<0.001). and Vitamin D was positively correlated with eGFR and it is statistically significant. (p<0.001).

## DISCUSSION

In present study, 90 CKD patients were taken up for study to determine the vitamin D , PTH, TNF-α and carotid artery intima media thickness. CKD patients are divided in to Group I (CKD stage 1 & stage 2), Group II (CKD Stage 3 & Stage 4) and Group III (CKD Stage 5) each Group contains 30 subjects each. Investigations were carried out and relevant information were gathered and tabulated.

In the present study Age and sex matched individuals are taken in all Groups. In the present study the mean blood urea in Group I, Group II and Group III were 40.76±11.36, 66.96±21.36 and 115.23±18.13 respectively and the increased level of blood urea is statistically significant (p<0.0001). In the present study the mean Serum Creatinine in Group I, Group II and Group III were 1.30±0.18, 2.65±0.68 and 6.14±0.39 respectively and the increased level of serum creatinine is statistically significant (p<0.0001). In the present study the mean estimated GFR in Group I, Group II and Group III were 77.18±7.15, 28.67±11.54 and 9.65±1.07 respectively and the decreased eGFR is statistically significant (p<0.0001). The increased blood urea and serum creatinine in CKD patients is due to decline in glomerular filtration. eGFR based on serum creatinine will provide accurate results. Ifeoma et al, study was also shown same findings [19].

In the present study the mean serum calcium in Group I, Group II and Group III were 8.70±0.43, 8.57±0.21 and 7.78±0.86 respectively and the decreased level of serum calcium is statistically significant ($p<0.0001$). In the present study the mean Serum Phosphorus in Group I, Group II and Group III were 4.33±0.32, 4.96±0.53 and 5.58±0.37 respectively and the increased level is statistically significant ($p<0.0001$). In the present study the mean serum Vitamin D in Group I, Group II and Group III were 30.90±3.95, 24.70±3.26 and 21.10±3.03 respectively and the decreased level is statistically significant ($p<0.0001$). In the present study the mean Serum PTH in Group I, Group II and Group III were 83.06±11.12, 104.93±13.83 and 219.87±37.98 respectively and the increased level is statistically significant ($p<0.0001$). In the present study the mean Serum TNF-α in Group I, Group II and Group III were 17.03±2.37, 30.60±4.65 and 48.13±5.99 respectively and the increased level is statistically significant ($p<0.0001$).

Serum calcium level was declined as CKD progress due to the retention of phosphate and declined calcitriol and decreased to the calcaemic action of parathyroid hormone on bone. Calcium is a key molecule for regulation of PTH secretion via specific membrane receptor, which is present chief cells of the parathyroid gland surface [20]. As CKD Progress the serum calcium level will be decreases due to retention of phosphate. Decreased vitamin D and resistance to action of PTH on bone causes alteration of calcium. PTH secretion inversely with calcium. In CKD due to decreased calcium receptors causes inadequate suppression of PTH secretion resulting high PTH [21].

As CKD progresses, glomerular filtration rate decreases which leads to declined phosphate filtration [22]. It plays main role in development of secondary hyperparathyroidism [23]. Various theories explained how retention of phosphate causes release of PTH that includes induction of hypocalcaemia, declined formation of active calcitriol and directly increased phosphate causes raise gene expression of PTH [24, 25]. Based on above theory decreased free calcium and calcitriol and phosphate retention in early CKD contribute hyperparathyroidism [26, 27]. Calcitriol level decreases below the normal if GFR is less than 30ml/min. In previous studies also reorted that calcitriol level decreased below the normal in mild to moderate CKD [28]. Tumor necrosis factor (TNF) α is a one of the most important proinflammatory cytokine and also causes inflammatory tissue damage. Tumor necrosis factor also has immune-regulatory functions. Clinical studies and experimental studies revealed the pathogenesis of TNF role in the acute and chronic kidney disease. In Chronic kidney diseases TNF mediate both proinflammatory and immunosuppressive effects. Recent Experimental data showed a specific role of the TNF mediating local inflammatory injury in the kidney [29].

In the present study the mean CIMT left side in Group I, Group II and Group III were 0.73±0.05, 0.82±0.05 and 0.84±0.04 respectively and the increase is statistically significant ($p<0.0001$). The mean CIMT right side in Group I, Group II and Group III were 0.71±0.04, 0.81±0.05 and 0.85±0.04 respectively and the increase is statistically significant ($p<0.0001$). The mean CIMT in Group I, Group II and Group III were 0.72±0.04, 0.82±0.05 and 0.85±0.04 respectively and the increase is statistically significant ($p<0.0001$). Lu Xia Zhang et al, study reported that in CKD stage II and III CIMT was significantly raised and concluded the progression CKD will causes arterial change.[30] Preston et al, shown that Stage III and IV have raised CIMT compared with Normotensive [31]. Atherosclerotic changes in carotid arteries might be indicative of atherosclerosis of coronary arteries [32]. CIMT is a non-invasive marker for generalized atherosclerosis and good indicator for coronary heart disease. Declined kidney function leads to decreased vitamin D synthesis [33].

In the present study correlation of TNF-α and Vitamin D with eGFR was conducted. In Group I TNF-α and Vitamin D were not correlated to eGFR and it is not statistically significant. In Group II TNF-α ($r= -0.59629$) was negatively correlated with eGFR and it is statistically siginificant ($p<0.001$) Whereas Vitamin D was not correlated to eGFR. In Group III TNF-α ($r=-0.84697$) was negatively correlated with eGFR and it is statistically significant. ($p<0.001$) Whereas Vitamin D ($r=0.94626$) was positively correlated with eGFR and it is statistically significant. ($p<0.001$).

Vitamin D inhibit cyclin-dependent kinase-2 activity and further causes suppression vascular smooth muscle cell proliferation [34]. TNF induces inflammation and bone remodelling. In this study mean serum calcium and Vitamin D were lowered in later stages of CKD Groups. Whereas serum phosphate, parathyroid hormone serum TNF level were increased in later stages of CKD Groups.

In summary, we observed that Calcium, Vitamin D decreased in CKD Groups, whereas, serum Phosphate, PTH and Serum TNF-α levels showed an increase. In Group II and Group III Serum TNF-α was negatively correlated and in Group III vitamin D positively correlated with eGFR. CKD is due to profound inflammatory changes with hypocalcaemia, hyperphosphataemia, hypovitaminosis D, and secondary hyperparathyroidism.

## CONCLUSION

This study can support the utilization of TNF-*α* and Vitamin D as early alarming markers during the early stages of CKD. Their estimation can provide an insight into the prevention of the rapid progression of CKD. The progression and complications of CKD, especially the cardiovascular complications can be prevented or at least postponed to some extent. Elevated circulating levels of TNF-*α* could be useful in risk stratification and also, could be potential therapeutic targets.

**Conflict of interest:** No conflict of interest**.**

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