



# CHRONIC KIDNEY DISEASE (CKD); RELATIONSHIP BETWEEN VITAMIN D LEVEL AND INFLAMMATORY MARKERS. 4 PTS A SINGLE CENTRE STUDY.

Adil Manzoor<sup>1</sup>, Rashid Abasher<sup>2</sup>

1. MBBS, FCPS (Nephrology)  
MRCP (Gen. Med), FRCP (Glas)  
Consultant Nephrologist  
King Fahd Hospital, Saudi Arabia.
2. MBBS  
Resident  
Department of Nephrology,  
King Fahd Hospital, Saudi Arabia.

**Correspondence Address:**  
Dr. Adil Manzoor  
Clinical Director of nephrology  
King Fahd hospital Madina  
dl\_manzoor@yahoo.com

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**ABSTRACT... Introduction:** Vitamin D deficiency is pretty common among the patients with CKD some studies suggesting it to be starting from CKD 3 when the egfr start falling from 60 ml/min. The cause can be due to different reasons including race, obesity, nutrition, lack of exposure to sun, and not the least, decrease in 1, alpha hydroxylase once the gfr starts to fall significantly. **Objectives:** The hypothesis was that lower Vitamin D level will be associated with increased inflammatory burden and decreased immunological response. **Study Design:** This was a cross-sectional study looking at the relationship between Vitamin D level and inflammatory markers in CKD 4 Pts when egfr started falling from 30 ml/min. **Study Design and Duration:** The study was started in March 2016 and finished in May 2016 among consecutive 100 CKD 4 patients coming to the clinic who were identified to be eligible for the study. **Materials and Methods:** We looked at the relationship between Vitamin D level and markers of mineral bone disorder, similarly we also looked at the relationship between erythropoietin dosage, hemoglobin and Vitamin D levels. Erythropoietin dose, hemoglobin, transferrin saturation, were used to study the link between Vitamin D and markers of anemia. Hepatitis B surface antigen antibodies were measured to study the response between Vitamin D level and immune response to Hep B vaccine. **Results:** Vitamin D levels were significantly lower in diabetics compared to non-diabetics (P = 0.02) and lower in females compared to males (P = 0.009). No statistical significance was observed between Vitamin D levels and immune response to hepatitis B vaccine (P = 0.89), phosphate level (P= 0.1), calcium levels (P = 0.79), parathyroid hormone (PTH) levels (P = 0.57), C-reactive protein (P=0.19), serum albumin (P = 0.17), hemoglobin level (P = 0.18,) and erythropoietin requirement (P = 0.87). **Conclusions** Vitamin D deficiency is highly prevalent in advanced CKD in Saudi Arabia. A RCT is recommended regarding response to vitamin D supplementation.

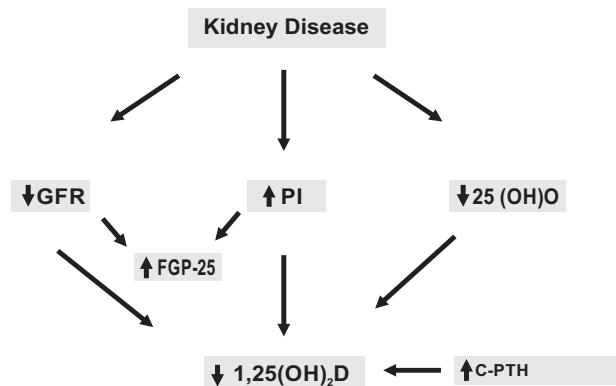
**Key words:** Vitamin D, Inflammatory Markers and CKD.

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## INTRODUCTION

Vitamin D is a lipid soluble and has a specific receptor. It is involved in the regulation of the human genome.<sup>1</sup> Vitamin D deficiency is quite common. Experts have defined vitamin D deficiency as serum Vitamin D levels less than 20 and insufficiency between 21 and 29ng/ml which translates that levels greater than that is needed for optimal health.<sup>2,3</sup> It is estimated that nearly 100 million people worldwide have Vitamin D deficiency.<sup>4</sup> in recent studies, 20-60% of normal individuals have Vitamin D deficiency. This problem is further exacerbated in patients with advanced CKD, and evidence suggests that 70 -80 percent<sup>5,6</sup> of this population is deficient. The cause can be because of variety of reasons

including poor nutritional intake, lack of sunlight, race, obesity, aging, loss of appetite<sup>7</sup> specially in relation to advanced CKD and not the least, impaired Vitamin D synthesis.



In Chronic kidney disease the osteocyte derived hormone FGF 23 which increases phosphate excretion is increased to compensate for phosphate retention and inhibits renal one alpha hydroxylase expression and it increases the expression of 24-hydroxylase responsible for the breakdown of 1,25-(OH)<sub>2</sub>D. 24,25(OH)<sub>2</sub>D levels are however lower in maintenance dialysis pts than the normal healthy individuals. The impaired uptake of 25(OH)D, once the renal disease starts to worsen remains the most important cause of 1,25(OH)<sub>2</sub> deficiency, as the metabolism of calcitriol does not seem to be altered. Added to this effect of high 25(OH)D levels, local osteoblastic conversion of 25(OH)D to 1,25(OH)<sub>2</sub>D appears to be an important positive regulator of FGF-23 production particularly in pts with end stage renal disease.<sup>8</sup> Vitamin D3 resistance has been found in CKD and was associated with progressive decline in renal functions. In addition to the calcitriol defective metabolism, up regulation of renal klotho expression may play a part in the progressive renal disease and cardiac disease in CKD pts.<sup>9,10</sup> Vitamin D is imperative in calcium and phosphate homeostasis and bone metabolism. Vitamin D deficiency leads to conditions such as, rickets, osteomalacia, osteoporosis, hyper parathyroid bone disease and fractures. Vitamin D has been found to have extra skeletal functions also including heart, brain, kidneys, and the immune system.<sup>11</sup> The nephroprotective effect of Vitamin D through various mechanisms,<sup>12-14</sup> has also been described and more importantly, it has been implicated in the progression of chronic kidney disease.<sup>15,16</sup> Vitamin D deficiency has been associated with increased cardiac mortality,<sup>17-19</sup> malignancy<sup>20,21</sup>, increased mortality in chronic kidney patients<sup>22</sup>, depression, maintenance of cognitive function,<sup>23-25</sup> and autoimmune conditions,<sup>26,27</sup> Vitamin D and systemic inflammatory processes has been found to be related to each other and it plays an important role in dendritic cells, macrophages, T-cells, and B-cells<sup>28,29</sup>, regarding their regulation, proliferation, differentiation, and their function. Studies examining link between Vitamin D deficiency and biomarkers of inflammation have shown a positive association.<sup>30-32</sup> Vitamin D replenishment was found to improve

inflammation.<sup>33</sup>

Similarly in CKD pts treatment with the activated forms of vitamin D has been shown to decrease proteinuria, and in some trials a reduction in blood pressure.<sup>34</sup> The studies examining the relationship between Vitamin D and inflammatory markers have excluded patients with advanced CKD. We asked the question, was lower Vitamin D level associated with increased inflammatory burden and decrease immunological response to Hep B vaccination in CKD 4 pts. We also decided to look at the relationship between Vitamin D level and markers of CKDMBD and anemia.

## MATERIALS AND METHODS

It is a cross-sectional study looking the relationship between Vitamin D level and inflammatory markers and markers of mineral bone disorder and hemoglobin and erythropoietin dose in CKD 4 pts.

## INCLUSION CRITERIA

All consecutive patients coming to the clinic with CKD 4 with eGFR less than 29 and greater than 15 were included in the study.

## Exclusion criteria

All patients who were admitted in the hospital at the time of study or patients with active infection or malignancy were excluded from the study plus all the pts who were CKD 5 or CKD 5D who initiated the dialysis were excluded from the study.

## Patient selection

A total of 100 patients were identified to be eligible for the study. The study was started in March 2016 and finished in May 2016.

Vitamin D deficiency was defined as total 25 hydroxy Vitamin D level <10 ng/mL, level between 10 and 29 defined insufficiency, and level ≥ 30 was regarded as normal.

CRP and albumin were the parameters for inflammation. Regarding anaemia markers Hemoglobin, transferrin saturation (TSAT), and erythropoietin dose were used.

Hepatitis B surface antigen antibodies were measured to see the response between Vitamin D level and hepatitis B vaccines immune response. Intact parathyroid hormone (PTH) assay was done by in vitro chemiluminescent micro particle immunoassay for the quantitative determination of intact PTH in serum.

**Confidentiality**

All data were stored and evaluated in password protected computers.

Sex; Male (%)	49
Age: Years	50(45 – 55)
Mean egfr	20(15 -26)
Diabetes (%)	41
Vitamin D (ng/mL)	11(9 – 14.5)
Hb (g/dL)	10(10 – 11.7)
TSAT (%)	24(20 – 37.5)
CRP	14(6 – 33.9)
Albumin	35(34 – 39)
Calcium (mmol/L)	2.2(2.06 – 2.39)
Phosphate (mmol/L)	1.8(1.4 – 2.11)
PTH	495(306 – 1034)
Darbepoetin dose/weekly	40 ug(40-80)

**Table-I. Baseline characteristics of study population.**

All results are median and IQR unless otherwise stated. CRP: C-reactive protein, IQR: Interquartile, PTH: Parathyroid hormone, TSAT; transferrin saturation.

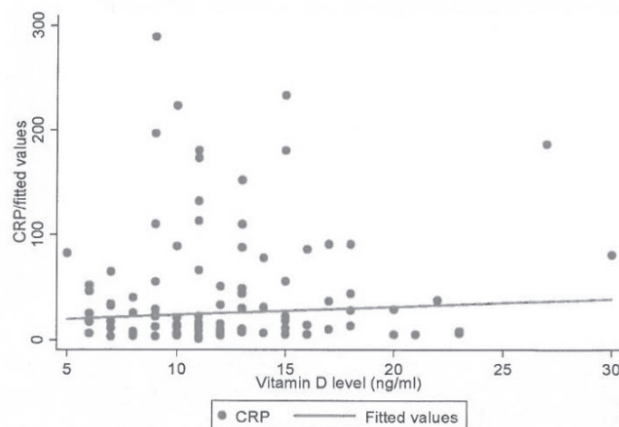
**Data Analysis**

Data were analyzed using Stata version 11. Median and interquartile (IQR) range was used to describe quantitative variables with asymmetrical distribution. Mean and standard deviation were used for quantitative variables with symmetrical distribution. Quantitative variables were analyzed using Student’s t-test or Wilcoxin rank-sum test depending on distribution of the variables. Categorical variables were analyzed using Chi-square test. Linear regression was used to analyze relationship between quantitative variables.

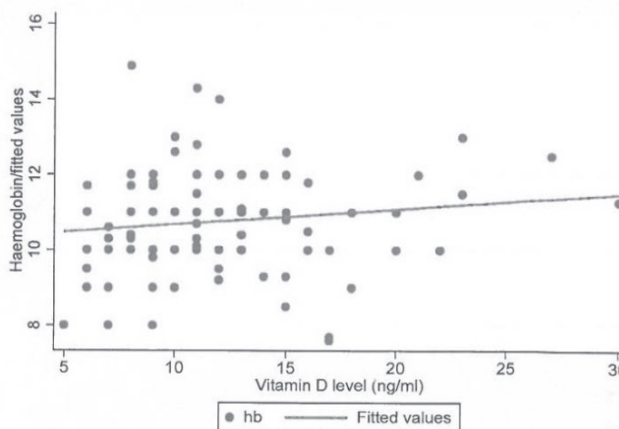
**RESULTS**

One hundred CKD 4 patients (49 males, fifty one females) with a median age of 50 years (IQR 44, 68) were studied (Table-I). Mean egfr was 20ml

range (15-26). Forty-one percent of the patients had diabetes.



**Figure-1. Relation between C-reactive protein and Vitamin D level.**



**Figure 2. Relation between hemoglobin and Vitamin D level.**

Vitamin D levels were lower in females as compared to males with a statistical significance (P = 0.009) Similarly diabetics had lower Vitamin D levels (P - 0.02) as compared to nondiabetics. CRP and Vitamin D levels (,P - 0.19, Figure-1) did show any association regarding its statistical significance. The association between Vitamin D level and serum albumin (P = 0.17) was also not significant. No significant association was found between Vitamin D levels and hemoglobin level (P = 0.18, Figure-2) or erythropoietin requirement (P = 0.87). No significant association was seen between Vitamin D level and antibody response to hepatitis B vaccine (P = 0 89). Calcium was also not associated with Vitamin D levels (P = 0.79). No significant association was found between

Vitamin D and phosphate level ( $P = 0.1$ ). No significant association was found between Vitamin D levels and PTH levels ( $P = 0.57$ ).

## DISCUSSION

This study highlighted the prevalence of Vitamin D deficiency among patients with CKD 4. 99% of patients had Vitamin D deficiency and insufficiency, which is significantly higher than previous reported studies.<sup>6,7</sup> Vitamin D levels were lower in females and diabetic population. CRP and Vitamin D levels did not show any significant association, similarly Vitamin D level and serum albumin did not show any significant association which is contrary to a previous study that showed that lower levels of albumin in CKD 5 Pts were associated with significantly lower Vitamin D levels.<sup>35</sup> Hemoglobin level, erythrocyte-stimulating agents dose and Vitamin D level also failed to show any significant association. In another study, lower Vitamin D levels were associated with increased inflammation but it was a very large study, with more than 700 pts. Another reason for not observing an association between markers of inflammation and Vitamin D levels in our study could be the narrow clustering of Vitamin D levels around their median. Two of these factors may lead to inadequate comparison between Vitamin D deficient, insufficient, and Vitamin D sufficient populations. CRP elevation is an unexplained phenomena among advanced CKD patients, and a number of pathophysiological mechanisms have been described such as an increase in cytokine production and retention<sup>36</sup> and also, the different types of dialyzer membranes were thought to play a significant role in inflammation.<sup>37</sup>

Study did not show any significant association between Vitamin D levels and markers of mineral bone disorders. Narrow clustering of Vitamin D and insufficient number of patients in the group with adequate Vitamin D levels may be the reason.

The recent discovery about Vitamin D that most cells in the body have Vitamin D receptors (VDRs) has revolutionized our concepts about the extra skeletal functions of vitamin D specially its role in regulation of the immune system. Vitamin D binds to VDR, which leads to the inhibition of pro-

inflammatory cytokines that reduces inflammatory response.<sup>38</sup> It is known that activation of VDR results in both up regulation and down regulation of important proteins, which are involved in inflammatory response. The levels of VDR become subnormal and CYP 24 A1 increases in CKD pts.<sup>39</sup> In addition vitamin D binding protein increases and is not involved in 25(OH) deficiency in CKD patients.<sup>40</sup> It has been found that vitamin D tubular absorption is suppressed due to decreased megalin.<sup>41</sup> As a compensatory mechanism Vitamin D catabolism is decreased in CKD pts and specially the patients on maintenance dialysis.<sup>42</sup> It is suggested that uraemic milieu causes a decrease in vitamin D synthesis secondary to PTH mediated fall in CYP450 isoforms<sup>43</sup> at the level of liver. It has been reported that muscular weakness and falls in patients on maintenance dialysis have been associated with vitamin D deficiency and it is a j curve with a maximal benefit is between 24 and 40 ng/ml of serum 25(OH)D levels.<sup>44</sup> It is reported that pts on maintenance haemodialysis show decreased production of cholecalciferol in the skin, despite of the normal content of dehydrocholesterol.<sup>45</sup> Vitamin D can selectively inhibit effect functions of interferon- $\gamma$  (INF- $\gamma$ ) activated macrophages and thereby, inhibition of IFN- $\gamma$ -induced genes which are very important regarding the inflammatory actions of macrophages when they are activated.<sup>46</sup>

Previous studies looking at the link between Vitamin D and inflammatory markers have excluded pts with CKD. Few studies done in a dialysis population did show that Vitamin D replenishment attenuates inflammation.<sup>47,48</sup>

Similarly studies of transplant pts showed high percentage of vitamin D49 deficiency, observational studies showed Vitamin D deficiency increases as the CKD progresses.<sup>50</sup> In one study vitamin D deficiency was found to be the same in CKD pts and general population.<sup>51</sup> In chronic haemodialysis pts<sup>52</sup> obesity and metabolic syndrome were associated with vitamin D deficiency. Cognitive decline<sup>53</sup> has been associated with vitamin D deficiency in Peritoneal dialysis pts. Low vitamin D levels have been associated with rapid worsening of renal

functions<sup>54,55</sup> in the transplant population. The nephroprotective effect of vitamin D has been due to suppression of renal angiotensin axis and NF-KB axis. Similarly up regulation of nitric oxide synthase transcription in vascular endothelial cells<sup>56,57</sup> has been reported. In one metanalysis it was reported that higher vitamin D level was associated with a decrease in mortality.<sup>58</sup> CKD prognosis do improve with vitamin D supplementation. Low vitamin D have been associated with increased mortality in dialysis pts. In a french cohort mortality was increased when the serum 25(OH) fell less than 20ng/ml.<sup>59</sup> The relationship between vitamin D and outcomes should be seen in conjunction with FGF 2360 and serum PTH.

In Saudi Arabia this is the largest study looking at the prevalence of Vitamin D deficiency in advanced CKD and looking at the association between Vitamin D deficiency and inflammatory markers and anemia.

## CONCLUSIONS

Vitamin D deficiency is highly prevalent in advanced CKD in Saudi Arabia. A RCT is recommended regarding response to vitamin D supplementation.

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**AUTHORSHIP AND CONTRIBUTION DECLARATION**

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
1	Adil Manzoor	1st Author	
2	Rashid Abasher	2nd Author	