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EFFECT OF VITAMIN D SUPPLEMENTATION ON INFLAMMATORY MARKERS IN PATIENTS WITH END-STAGE RENAL DISEASE

[*1]Rasha Saad Sharad, [2]Ahmed Fadhil Alkafagi, [3]Jawad Ibrahim Al-Sharif

[1]Al-Najaf Health Directorate, Al-Najaf, Iraq.
[2]Director of Artificial Kidney, Medical City, Baghdad, Iraq.
[3]Internist-Nephrologist, Medical City Complex.

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***Corresponding Author: Rasha Saad Sharad**
Al-Najaf Health Directorate, Al-Najaf, Iraq.

ABSTRACT

Background: Chronic kidney disease (CKD) and end-stage renal disease (ESRD) are associated with persistent inflammation and oxidative stress, which contribute to adverse outcomes. Vitamin D deficiency is common in ESRD patients and is thought to exacerbate inflammatory processes. **Objective:** This study aimed to evaluate the impact of vitamin D supplementation on inflammatory markers in ESRD patients with vitamin D deficiency. **Methods:** A cross-sectional study was conducted on 100 ESRD patients undergoing hemodialysis at the Iraqi Center of Dialysis, Baghdad Teaching Hospital, between September 2023 and December 2024. All participants had vitamin D levels <20 ng/mL, elevated parathyroid hormone (>300 pg/mL), and hypocalcemia (<8.5 mg/dL). Patients were divided into two groups: one received vitamin D supplementation, and the other received a placebo for four weeks. Inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and interleukin-6 (IL-6), were measured pre- and post-intervention using ELISA. **Results:** Following vitamin D supplementation, significant reductions were observed in CRP (from 1.67 ± 0.15 to 1.01 ± 0.1 mg/dL), ESR (from 33.4 ± 10.5 to 21.4 ± 9.8 mm/hr), and IL-6 levels (from 59.9 ± 15.8 to 41.2 ± 12.2 pg/mL) ($p < 0.05$ for all). These findings support vitamin D's potential anti-inflammatory role in ESRD. **Conclusion:** Vitamin D supplementation significantly reduces key inflammatory markers in ESRD patients with vitamin D deficiency. Further large-scale, randomized controlled trials are warranted to confirm these findings and explore long-term outcomes.

KEYWORDS: Vitamin D, Inflammatory, Markers, End-Stage, Renal Disease.

INTRODUCTION

Chronic kidney disease (CKD) is a leading cause of death in underdeveloped nations.[1] Increased oxidant mediator due to uremia, increased oxygen metabolism, increased inflammatory factors, iron therapy, dialysis procedure, lack of antioxidant vitamins and microelements, malnutrition, and renal replacement therapy-related factors all contribute to oxidative stress.[2] Although oxidative stress arises as a result of an enhanced inflammatory response, low blood levels of 25-hydroxyvitamin D (25(OH)D) have been linked to elevated inflammation indicators.[3] Vitamin D, as a steroid hormone, is well known for its function in calcium, phosphorus, and bone metabolism modulation. It is 25-hydroxylated in the liver before being 1-alpha-hydroxylated to its active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$), by 1-alpha-hydroxylase in the kidney. The effects of vitamin D have been proven in various organs, including the immune system, where $1,25(OH)_2D$ reduced cytokine production.[4] Vitamin D insufficiency causes illnesses such as hyperparathyroid bone disease, rickets, osteomalacia, osteoporosis, and fractures due to its function in the control of calcium and phosphate and hence bone metabolism.[5] However, a growing body of data from research suggests that vitamin D has biological impacts beyond calcium and phosphate balance, and that vitamin D level is critical for proper function of numerous organs, including the kidneys, heart, brain, and immune system.[6] Chronic inflammation and low 25(OH)D levels in the blood are frequent among CKD patients, and they are linked to poor outcomes. The causes of hypovitaminosis D or impaired vitamin D metabolism in end-stage renal disease (ESRD) are unknown, although they may include decreased glomerular filtration rate, restricted sunshine exposure, and decreased Ultraviolet-B-induced vitamin D synthesis in the skin.[7] Oxidative stress and inflammation both have a role in the development of

CKD. It has been found that following HD, antioxidant enzymes increase while oxidation indicators decrease. Vitamin D treatment has been shown to successfully reduce oxidative stress and inflammation. Several methods have been proposed to explain vitamin D's influence on inflammatory markers.[8] Vitamin D has been shown to reduce inflammation by increasing nitric oxide (NO) production and lowering free radical generation. Vitamin D produces a considerable increase in NO production by activating its receptor and NO synthase.[9] Another possible mechanism is an increase in plasma 25(OH)D concentration after vitamin D intake. This increase in plasma 25(OH)D concentration would then enhance intestinal calcium absorption, potentially leading to higher intracellular calcium levels, which would drive NO generation.[10] Vitamin D may also reduce inflammation by lowering blood pressure. This happens by blocking the nuclear factor-kappa B (NF-kB) pathway and reducing the production of renin and angiotensinogen genes through a vitamin D response element in the part of the renin gene that controls its activity. This study aims to assess vitamin D supplementation's impact on inflammatory markers in end-stage renal disease patients.

METHOD

The current cross-sectional study included 100 ESRD patients with vitamin D deficiency. Patients were recruited from Iraqi center of dialysis/Baghdad teaching hospital/Medical City/Baghdad. Patients were in the duration of 4 weeks between September 2023 to December 2024. After recruitment of patients, verbal consent was acquired from patients. Formal approvals were obtained from scientific committee of Arab board of health & specializations. Inclusion criteria: ESRD patients with vitamin D deficiency (less than 20 ng/ml), hyperparathyroidism (more than 300 pg/mL) and hypocalcaemia (less than 8.5 mg/dl) were included. Exclusion criteria: Pediatric age group, normal vitamin D level, parathyroid hormone < 300 pg/mL, calcium level > 8.5 mg/dl, Patients diagnosed with malignancy.

Patients were subjected to the following.

- Full personal history recording including: patients' age, gender, duration and family history of renal disease.
- Clinical data including blood pressure, body mass index and drug history.
- Routine laboratory work-up including serum alkaline phosphatase, serum albumin, serum creatinine, serum phosphorus, Hg A1c and estimated glomerular filtration rate (eGFR) were assessed.
- Patients were divided into 2 groups cases and controls; cases were administered vitamin D while controls were administered a placebo.
- Treatment was administered the study duration of 4 weeks.
- Assessment of inflammatory markers in patients before and after vitamin D supplementation including Erythrocyte Sedimentation Rate (ESR), C-reactive protein (CRP) and interleukin-6 (IL-6). Measurement was preformed using Enzyme Linked Immunosorbent Assay (ELISA) according to manufacturer's instructions.

Statistical analysis: Data was presented as frequencies and proportions. Analysis was completed using SPSS version 25. Pearson Correlation analysis was performed to assess the strength of association between two quantitative variables. The correlation coefficient defines the strength and direction of the linear relationship between two variables.

RESULTS

The current study included 100 ESRD patients with vitamin D deficiency (less than 20 ng/ml). Included patients were 55 females and 45 males with mean age 59 ± 11.1 years. Mean duration of dialysis was 7.8 ± 2.3 years. Of the included patients, 23 had positive history of renal disease (Table 1).

Table 1: Demographic data of included patients.

Gender (No.)	**Male**	**55**
	Female	**45**
Age (years)	Mean ± SD	59 ± 11.1
Duration of dialysis (years)	Mean ± SD	7.8 ± 2.3
History of renal disease	Positive	23
	Negative	77

Mean BMI in included patients was 25.36 ± 3.78, mean systolic blood pressure was 153.13 ± 12.3 mmHg while mean diastolic blood pressure was 85.39 ± 6.7 mmHg (Table 2).

Table (2): Clinical features of the included patients.

BMI	**Mean ± SD**	**25.36 ± 3.78**
Systolic BP (mmHg)	Mean ± SD	153.13 ± 12.3
Diastolic BP (mmHg)	Mean ± SD	85.39 ± 6.7
Drug history (No.)	Antiplatelet Drugs	70
	Statins	45
	RAS inhibitors	55

Laboratory work-up of included patients was illustrated in table 3. Mean level of alkaline phosphatase was 127.6 ± 9.6 mg/dL, serum albumin 3.92 ± 0.51 g/dL, serum creatinine 16.3 ± 1.12 mg/dL. In addition, estimated glomerular filtration rate (eGFR) was 14.08 ± 3.16 ml/min/1.73m^2, serum phosphorus was 4.81 ± 0.9 mg/dL and Hg A1c was 6.3 ± 2.9%.

Table (3): Laboratory work-up of included patients.

ALP (mg/dL)	Mean ± SD	127.6 ± 9.6
Albumin (g/dL)	Mean ± SD	3.92 ± 0.51
Creatinine (mg/dL)	Mean ± SD	16.3 ± 1.12
eGFR (ml/min/1.73m^2)	Mean ± SD	14.08 ± 3.16
Phosphorus (mg/dL)	Mean ± SD	4.81 ± 0.9
Hg A1c (%)	Mean ± SD	6.3 ± 2.9

Assessment of inflammatory markers in patients before and after vitamin D supplementation revealed significantly decreased CRP, ESR and IL-6 after vitamin D supplementation compared to before treatment (Table 4).

Table (4): Assessment of inflammatory markers in patients before and after vitamin D supplementation.

		Before vitamin D supplementation	After vitamin D supplementation	P value
CRP (mg/dL)	Mean ± SD	1.67 ± 0.15	1.01 ± 0.1	< 0.05 (S)
ESR (mm/hr)	Mean ± SD	33.4 ± 10.5	21.4 ± 9.8	< 0.05 (S)
IL-6 (pg/ml)	Mean ± SD	59.9 ± 15.8	41.2 ± 12.2	< 0.05 (S)

Using Paired t test, p value < 0.05 is significant

DISCUSSION

This study involved a cohort of 100 patients with end-stage renal disease (ESRD) who presented with vitamin D deficiency. Following vitamin D supplementation, a significant reduction was observed in inflammatory markers, including CRP, ESR, and IL-6, compared to pre-treatment levels. Vitamin D deficiency is common among patients with chronic kidney disease (CKD), particularly those undergoing renal replacement therapies such as hemodialysis and peritoneal dialysis. Numerous investigations have explored the relationship between vitamin D status and inflammatory markers (CRP, ESR, IL-6), but the findings have often been inconsistent and inconclusive. Several studies support a link between low vitamin D levels and elevated inflammatory markers in renal failure patients. Vitamin D has demonstrated anti-inflammatory effects through its regulation of immune responses. Harishankar et al. reported that 1,25-dihydroxy vitamin D3 downregulated pro-inflammatory cytokine responses, indicating its immunomodulatory potential in infectious conditions like tuberculosis, which may extrapolate to renal disease states as well.[12] Similarly, a systematic review and meta-analysis by Mazidi et al. found that vitamin D supplementation was associated with reduced CRP levels, suggesting a possible role in modulating systemic inflammation.[13] Conversely, a meta-analysis by Zhao et al. concluded that vitamin D supplementation did not lead to statistically significant reductions in CRP and IL-6 in CKD patients when compared to controls, suggesting that the effect of vitamin D on inflammatory markers remains uncertain. The authors emphasized the need for larger and more rigorously designed trials to reach definitive conclusions.[14] Etminan et al. studied ESRD patients and found a significant inverse correlation between 25(OH)D3 levels and ESR. However, associations with CRP and IL-6 were not statistically robust, highlighting the variability in inflammatory responses among this population.[15] In a related study, Souza et al. observed a significant association between lower vitamin D levels and elevated ESR in hemodialysis patients, and also found increased IL-6 levels in those with vitamin D deficiency, supporting the link between vitamin D status and inflammation.[16] While some trials like those by Beilfuss et al. have demonstrated reductions in pro-inflammatory cytokines such as IL-6 and TNF-α following cholecalciferol supplementation[17], others such as Jiang et al. failed to show such benefits, suggesting a more complex interaction between vitamin D and inflammatory pathways.[18] The variability may depend on baseline vitamin D status, dosage, duration of supplementation, and heterogeneity in CKD pathology. Furthermore, de Medeiros Cavalcante et al. noted that vitamin D3 megadose supplementation significantly reduced inflammatory markers and oxidative stress in elderly women with vitamin D insufficiency, indicating potential benefits in specific subgroups.[19] These immunomodulatory effects of vitamin D underscore its therapeutic potential, though outcomes are not universally consistent across all renal populations.

CONCLUSION

while a correlation exists between vitamin D levels and inflammatory markers like CRP, ESR, and IL-6 in patients with renal failure, the clinical efficacy of vitamin D supplementation in mitigating inflammation remains controversial. Larger, high-quality randomized controlled trials are necessary to clarify vitamin D's role in inflammation management among CKD patients.

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