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RESEARCH ARTICLE

Evaluating the role of vitamin D metabolites and intact parathyroid hormone across chronic kidney disease stages

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Background: Chronic kidney disease (CKD) is defined as abnormal kidney structure or function that last over three months. Its prevalence increases with age, affecting 38% of individuals aged 65 years and older. Key biomarkers for assessing CKD severity include a low estimated glomerular filtration rate (eGFR) and increased albumin levels in urine, determined by the albumin-to-creatinine ratio (ACR). 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D are impaired in CKD patients due to reduced renal function, leading to deficiencies in active vitamin D forms and contributing to secondary hyperparathyroidism (SHPT). This study evaluated the role of vitamin D metabolites and intact parathyroid hormone levels in different stages of CKD.

Subjects and Methods: This cross-sectional study was performed at the Al-Imam Al-Sadiq Hospital in Babil, Iraq. This study included 164 patients (84 males and 80 females) with CKD stages 2-5. Patients were divided into groups based on CKD stage: 20 patients with stage 2 and 36 patients with stages 3a, 3b, 4, and 5. Blood samples were collected for the serum analysis of urea, creatinine, 25 (OH) D, 1,25 (OH)2 D, and intact PTH levels. Urine samples were collected to assess microalbuminuria. ELISA was used for vitamin D and PTH measurements, while standard biochemical methods were employed for the other parameters.

Results: 1,25 (OH)2 D and 25 (OH) D levels significantly declined with advancing CKD stage ($p \leq 0.001$), while iPTH levels increased significantly ($p \leq 0.001$). The 1,25VitD/iPTH ratio decreased significantly across the CKD stages ($p \leq 0.001$).

Conclusion: The study concluded an important association between deteriorating CKD (renal destruction), declining vitamin D metabolites (25 OH D, 1,25 OH D), and elevated iPTH levels.

Keywords: CKD, eGFR, 1,25 (OH)2 D, 25 OH D. iPTH

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Introduction

Chronic kidney disease (CKD) is a progressive condition characterized by abnormalities in kidney structure or function lasting over three months.[1]. The prevalence of CKD is higher in individuals aged ≥ 65 years, affecting 38% of this age group. In comparison, the prevalence is 13% among those aged 45-64 years and 7% among individuals aged 18-44 years. [2], African Americans have an approximately three-fold higher risk of developing End-Stage Kidney Disease (ESKD) than white people [3,4], and CKD prevalence is slightly higher in women (15%) than in men (12%) [2,5]. Studies on the worldwide prevalence of CKD estimate that 843.6 million people currently suffer from stages 1 to 5 of the illness. Stage 1 accounted for 3.5%, stage 2 accounted for 3.9%, stage 3 accounted for 7.6%, stage 4 accounted for 0.4%, and stage 5 accounted for 0.1% [6]. Key markers, such as estimated glomerular filtration rate (eGFR) and albumin-to-creatinine ratio (ACR), are commonly used to assess CKD severity [7]. Chronic kidney disease is associated with comorbidities, such as hypertension, diabetes, and cardiovascular disease, which further exacerbates kidney damage [8].

Vitamin D metabolism is profoundly affected in patients with CKD owing to impaired renal function. Cholecalciferol (vitamin D3) is converted in the liver to 25-hydroxyvitamin D [25(OH)D], which is subsequently hydroxylated in the kidney to 1,25-dihydroxy vitamin D [1,25(OH)2D], the active form of vitamin D [9]. However, CKD disrupts this process due to reduced renal mass and impaired activity of the enzyme CYP27B1, leading to decreased levels of 1,25(OH)2D [10]. Renal proximal tubular cells obtain 25 (OH) D for conversion to calcitriol, primarily from the glomerular ultrafiltrate, rather than from the bloodstream. Impaired renal absorption of 25 (OH) D in CKD significantly contributes to systemic calcitriol insufficiency and is a primary indicator of 25 (OH) D deficiency [11].

This deficiency contributes to secondary hyperparathyroidism (SHPT), a condition characterized by elevated parathyroid hormone (PTH) levels, which is a known risk factor for cardiovascular complications and bone disorders [12,13]. SHPT develops because of phosphate retention, reduced calcium absorption, and impaired vitamin D activation, which collectively increase PTH synthesis and secretion [14]. As a result, 1,25(OH)2D and the 1,25(OH)2D/PTH ratio could be significant risk factors for deterioration of renal function (WRF) [15]. The aim of

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this study was to evaluate the relationship between the levels of vitamin D metabolites (25 OH D and 1,25 (OH)2 D) and intact parathyroid hormone (iPTH) and CKD progression across different stages.

Materials and methods

Study Design and Participants

This cross-sectional study was conducted at Al-Imam Al-Sadiq Hospital in Babil, Iraq, between January 2023 and May 2024. The study included 164 patients (84 males and 80 females) diagnosed with CKD based on CKD criteria. Patients were categorized into CKD stages 2 to 5 according to the Kidney Disease: Improving Global Outcomes (KDIGO) 2012 guidelines, which use eGFR thresholds. The inclusion criteria included a confirmed CKD diagnosis lasting more than three months, while the exclusion criteria excluded individuals with primary hyperparathyroidism, previous parathyroidectomy, pregnancy, and lactation. This study strictly adhered to the institutional guidelines established by the College of Medicine at the University of Basra, and the Clinical Research Ethics Committee approved the protocol. The study was conducted in full compliance with scientific and ethical principles at the Al-Imam Al-Sadiq Hospital in Babylon. Informed consent was obtained from the patients or their relatives before inclusion in the study.

CKD Staging and eGFR Calculation

CKD staging was determined using the estimated glomerular filtration rate (eGFR) values. eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (2019 version) based on serum creatinine measurements standardized to isotope dilution mass spectrometry (IDMS) [16]. Patients were divided as follows: Stage 2 (eGFR 60-89 mL/min/1.73 m²), Stage 3a (45-59 mL/min/1.73 m²), Stage 3b (30-44 mL/min/1.73 m²), Stage 4 (15-29 mL/min/1.73 m²), and Stage 5 (<15 mL/min/1.73 m²).

Biochemical measurements

Blood samples were obtained from the patients by vein puncture. Blood (5 ml) obtained from each subject was dispensed in gel tubes and subjected to a clotting process for 20 min at room temperature (RT), followed by centrifugation at 3000 rpm for 20 min to separate the serum. Part of the serum that was used for estimation of urea and creatinine (kits supplied by BIOLABO/MALZY-FRANCE), and other aliquots were aliquoted into parts using Eppendorf tubes (0.5 ml) and stored at -20°C for subsequent analysis of 1,25 di OH vit D, 25 OH vit D, and intact PTH levels. iPTH was determined by sandwich ELISA following the manufacturer's recommendations (SunLong Biotech, China), while 1,25 (OH)2 D, 25 (OH) D levels were measured using the competitive ELISA protocol recommended by the manufacturer (BT LAB bioassay technology laboratory, China).

Urine samples were collected from each participant in the morning while they were still fasting in a disposable clean cap, transferred to a test tube, centrifuged (4–5 min) at 3000 rpm to remove any precipitate, and the supernatant was stored in a freezer for ACR. Urine creatinine was measured using a creatinine kit supplied by BIOLABO/MALZY-FRANCE and Albumin in urine was measured using Microalbumin Test cartridges supplied by Agappe Diagnostics (India).

Statistical analysis

Statistical analysis for this study was carried out using MedCalc statistical software and GraphPad Prism 9. One-way ANOVA was used to compare means for continuous variables across CKD stages, and chi-square tests were used to assess differences in proportions for categorical variables, with significant thresholds established at 0.05 and 0.01. These results emphasize the variability and progression of kidney function impairment, underscoring the utility of these biomarkers in monitoring and managing the disease. The figures in the study were meticulously illustrated using GraphPad Prism 9, facilitating a clear visualization of the data distribution and statistical outcomes.

Results

The age distribution of the 164 CKD patients was divided into five age groups (Table 1). This illustrates that most of these patients fell within the age brackets of 41-80. Specifically, the group aged 61-80 comprises 42.7% of the cases, making it the largest segment. This was followed by those aged 41-60 years (31.7%). Younger patients (under 20 years) constituted the smallest group, with only 4.9% of the cases.

Table 2 summarizes kidney function tests, vitamin D metabolites, and PTH levels in patients with CKD. eGFR averaged 35.07 ± 21.2 ml/min/1.73 m², while 25(OH)D and 1,25(OH)2D showed mean levels of 23.8 ± 9.7 µg/L and 1.5 ± 1.8 pg/ml, respectively. iPTH had a mean of 71.9 ± 48.6 pg/ml. The albumin-to-creatinine ratio (ACR) was 2168 ± 4540 mg/g.

Table 3 highlights the significant differences in vitamin D metabolites and iPTH levels across CKD stages. Both 25(OH)D and 1,25(OH)2D levels decreased progressively with CKD progression ($p < 0.001$ and $p = 0.002$, respectively), while iPTH levels showed a significant increase ($p < 0.001$). Figures 1 to 4 represent the differences.

Table 4 categorizes patients with various stages of CKD, based on their Vitamin D3 (25 Vit D) levels, into three

Table 1. Distribution of patients with chronic kidney disease according to their age groups

Age groups	CKD (n = 164)
< 20 Years	8 (4.9)%
21-40 Years	14 (8.5)%
41-60 Years	52 (31.7)%
61-80 Years	70 (42.7)%
> 81 Years	20 (12.2)%
Total	164 (100)%

Table 2. Kidney function test, vitamin D metabolites, and parathyroid hormone panel among patients with chronic kidney disease

Kidney function test panel	Minimum	Maximum	Mean	±SD
eGFR ml/min/1.73 m²	5	87	35.07	21.2
Blood urea (mg/dl)	28.8	252.6	97.2	51.5
Serum creatinine (mg/dl)	0.76	8.5	2.63	1.7
Urine creatinine (mg/dl)	5.8	593	78.9	95
Microalbumin (mg/dl)	0.5	289	72.85	87.8
ACR (mg/g)	2.98	33982	2168	4540
25 Vit D ug/l	9.0	55	23.8	9.7
1,25 Vit D pg/ml	0.047	12.1	1.5	1.8
iPTH pg/ml	4.0	227	71.9	48.6
1,25VitD /PTH ratio	0.0001	0.419	0.034	0.059

Table 3. Relationship between kidney function tests, vitamin D metabolites, and parathyroid hormone across different stages of chronic kidney disease

Kidney function test panel		Stage of CKD.					p
		Stage 2 (N. 20)	Stage 3a (N. 36)	Stage 3b (N. 36)	Stage 4 (N. 36)	Stage 5 (N. 36)	
eGFR (ml/min/1.73 m²)	Mean ±SD	73 ± 8.4	51.2 ± 4.3	36.6 ± 4.6	21.1 ±3.8	9.77 ± 2.7	<0.001 O***
Blood urea (mg/dl)	Mean ±SD	41.2 ± 12.2	67.8 ± 24.8	88.4 ± 39.9	102.9 ± 38	161 ± 42.5	<0.001 O***
Serum creatinine (mg/dl)	Mean ±SD	1.09 ± 0.12	1.35 ± 0.24	1.69 ± 0.32	2.9 ± 0.79	5.45 ± 1.35	<0.001 O***
urine creatinine (mg/dl)	Mean ±SD	138 ± 69	101 ± 53	54.8 ± 28	37 ± 24	29 ± 20.5	<0.001 O***
Microalbumin (mg/dl)	Mean ±SD	7.5 ± 6.9	25.3 ± 23.2	65.8 ± 88.7	107 ± 94.6	130 ± 97	<0.001 O***
ACR (mg/g)	Mean ±SD	60.9 ± 72	344 ± 430	1341 ± 2306	3955 ± 4354	8740 ± 11698	0.003 O**
25 VitD (ug/l)	Mean ±SD	36.6 ± 11.9	23.9 ± 10.6	23.5 ± 7.2	22.1 ± 6.4	18.56 ± 6.1	<0.001O***
1,25VitD (pg /ml)	Mean ±SD	3.2 ± 3.8	2.08 ± 1.9	1.3 ± 0.93	0.9 ± 0.36	0.76 ± 0.41	0.002 O**
iPTH (Pg/ml)	Mean ±SD	36.9 ± 9.9	42.7 ± 7.5	54.3 ± 16.2	72.5 ± 21.9	137.9 ± 62	<0.001O***
1,25 Vit D /iPTH Ratio	Mean ±SD	0.098 ± 0.13	0.051 ±0.05	0.03 ± 0.02	0.013 ± 0.008	0.006 ± 0.004	0.0003 O***

N: number of cases, SD: standard deviation, O: one-way ANOVA, **: significant at p ≤ 0.01, ***: significant at p ≤ 0.001

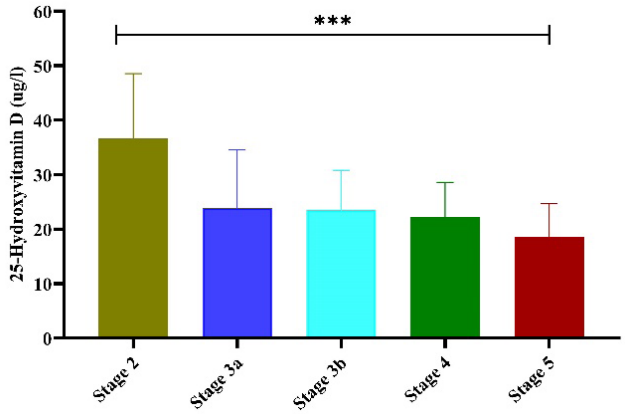

Fig. 1. Bar chart presenting the distribution of 25-hydroxyvitamin D levels among various stages of chronic kidney disease

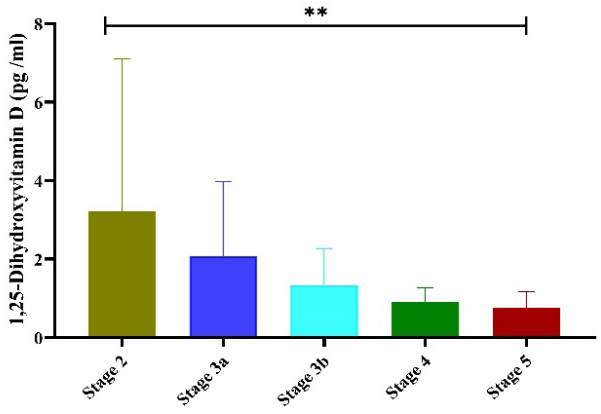

Fig. 2. Bar chart presenting the distribution of 1,25-dihydroxyvitamin D levels among various stages of chronic kidney disease

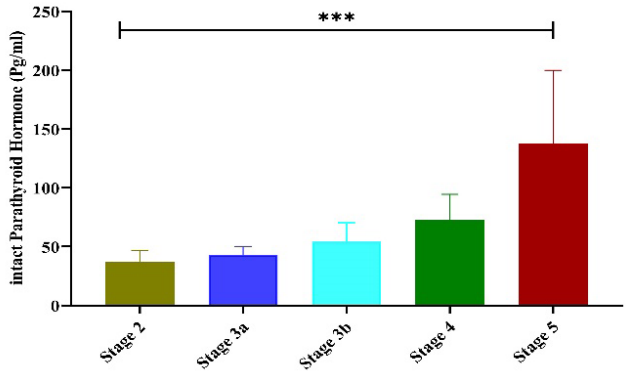

Fig.3. Bar chart presenting the distribution of intact parathyroid hormone levels among various stages of chronic kidney disease

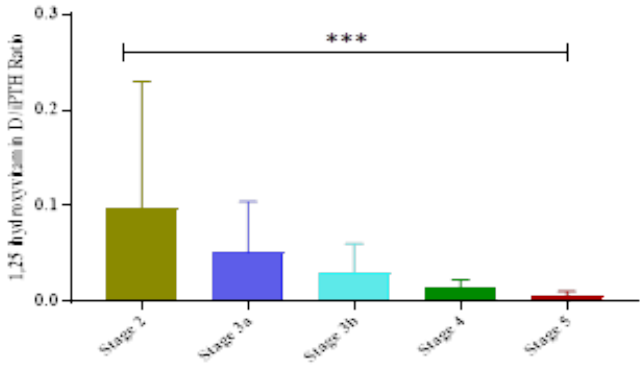

Fig. 4. Bar chart presenting the distribution of 1,25VitD /iPTH ratio levels among various stages of chronic kidney disease

Table 4. Distribution of 25 vit D levels across stages of chronic kidney disease

Vitamin D3 (25 Vit D) level		Stage of CKD.					Statistical inference
		Stage 2 (N. 20)	Stage 3a (N. 36)	Stage 3b (N. 36)	Stage 4 (N. 36)	Stage 5 (N. 36)	
Deficiency (Below 10 ug/l)	14 (8.5%)	0 (0 %)	0 (0 %)	2 (5%)	4 (11%)	8 (22%)	X2 = 50.1
Insufficiency (Below 10 - 30 ug/l)	116 (70.7%)	8 (40%)	22 (61%)	28 (78%)	30 (84%)	28 (78%)	< 0.001 C ***
Sufficiency (Above 30 ug/l)	34 (20.7%)	12 (60%)	14 (39%)	6 (17%)	2 (5%)	0 (0 %)	Significant

Chi-square test for case frequency was used to determine significance. Statistical significance was set at P ≤ 0.05.

categories: deficiency (below 10 ug/l), insufficiency (10-30 ug/l), and sufficiency (above 30 ug/l). Each stage of CKD (stages 2 through 5) displays a specific number of patients (N) and their corresponding percentage within each 25 Vit D category. The data show a trend where the proportion of patients with 25 Vit D deficiency increases and sufficiency decreases as the stage of CKD progresses. The statistical inference provided included a chi-square test value (X2 = 50.1) and a significance level ($p < 0.001$), indicating a highly significant variation in 25 Vit D levels across different CKD stages.

Discussion

The study revealed that most CKD patients fell within the age range of 41-80 years, with a significant difference of 42.7% in the 61-80 age group (Table 2). This finding aligns with broader research on CKD prevalence in older populations. Flaherty et al. (2024) [17] reported a substantial increase in CKD prevalence with age in the US, with estimates surpassing 50% for adults aged ≥ 70 years. Similarly, Mallappallil et al. (2014) [18] found a CKD prevalence of approximately 39.4% among US adults aged 60 years and older, attributing this high prevalence to increased risk factors for heart disease, diabetes, and high blood pressure. The disparity between these studies (>50% in the 70+ group vs. 39.4% in the 60+ group) underscores the rapid increase in CKD prevalence with advancing age. Further supporting these findings, data from the National Health and Nutrition Examination Survey (NHANES) 1999-2004 [19] indicated that the prevalence of CKD, evaluated using the CKD-EPI equation, was 46.8% among individuals aged ≥ 70 years, while it stood at 6.71% for those aged 40–59 years. The decline in kidney function associated with aging leads to gradual structural and functional alterations in kidneys. Additionally, the increased occurrence of risk factors, such as hypertension, diabetes, and cardiovascular illness, contributes to the elevated rates of CKD in older populations.

The study showed significant elevations in serum creatinine and blood urea levels across CKD stages ($p \leq 0.001$), consistent with other studies by Mehmood et al. (2022) [20], and Pandya et al. (2016) [21]. Serum creatinine and urea, nitrogenous end products of metabolism, accumulate with impaired renal function and serve as sensitive indicators of kidney dysfunction. Their utility is due to their biochemical properties and physiological handling, with urea indirectly measuring renal excretory function and creatinine correlating with the glomerular filtration rate (GFR). The findings of this study corroborate those of previous studies and highlight the complementary nature of these biomarkers in assessing renal function. The combined assessment of serum urea and creatinine levels enhances the sensitivity and specificity of kidney dysfunction detection and disease progression monitoring [20,21]

The study showed a clear decline in eGFR from CKD stage 2 to stage 5, aligned with the established understanding of CKD progression. Kaufman et al. (2018) [22] defined GFR as a quantitative measure of plasma flow from the glomerulus to Bowman's space, indicating kidney function. The European Medicines Agency (EMA, 2016) [23] Advocates for GFR as a comprehensive measure of renal function, even for drugs undergoing tubular secretion. GFR's clinical significance of GFR extends to CKD classification and staging, facilitating standardized communication among healthcare professionals. Nankivell BJ (2001) [24] Highlights GFR sensitivity in detecting renal impairment before clinical symptoms appear.

This study showed a significant decrease in 25-hydroxyvitamin D (25(OH)D) levels as CKD progresses ($p \leq 0.001$). Among 164 patients with CKD, 8.5% had deficient levels, 70.7% had insufficient levels, and only 20.7% had adequate amounts of 25(OH)D. These findings align with those of Bureo et al. (2015) [25] and De N and Oh DD. Erratum. (2019) [26] ; and Fernández-Juárez et al. (2013)The gradual decline in 25(OH)D levels across CKD stages is attributed to reduced sun exposure, dietary restrictions, and impaired cutaneous vitamin D synthesis in CKD patients.

The study showed that 1,25(OH)2D levels drop significantly at different stages of CKD ($p \leq 0.01$). Levin et al. (2007) [27] found that patients show low calcitriol levels even in early kidney dysfunction. Kim et al. (2022) [28] provided detailed data on the 1,25(OH)2D decline across CKD stages 3-5. The decline in 1,25(OH)2D levels is attributed to reduced renal mass and function, impaired 1α-hydroxylation, accumulation of uremic toxins, and metabolic acidosis, as explained by Al-Badr et al. (2008) [29]. Additionally, increased levels of fibroblast growth factor 23 (FGF23) suppress 1α-hydroxylase activity and enhance 1,25(OH)2D catabolism. Loss of renal klotho exacerbates this process by promoting FGF23 resistance and elevation. These factors collectively contribute to the progressive decline in 1,25(OH)2D levels observed across the CKD stages.

The study demonstrated a significant increase in iPTH levels as CKD progresses ($p < 0.0001$). This aligns with

the current understanding of parathyroid hormone dysregulation in CKD. Bureo et al. (2015) [25] showed that CKD patients had elevated PTH levels, which increased during the progression stages. Xu et al. (2021) [30] observed a dramatic increase in secondary hyperparathyroidism (SHPT) incidence with advancing CKD, which is linked to increased mortality and cardiovascular events, CKD progression, and fractures. Geng et al. (2019) [31] demonstrated PTH as a stand-alone indicator of worse outco4mes in individuals with CKD. This study explains the complicated pathophysiology behind high iPTH levels in CKD, which includes issues with calcium absorption, phosphate retention, and reduced calcitriol production. The study also found that the ratio of 1,25VitD to iPTH decreased significantly across CKD stages ($p \leq 0.001$). This is similar to what Galassi et al. reported in their PASCAL-1,25D study in 2022 [15].

Limitations and future directions

This study has several limitations. First, the cross-sectional design precludes the establishment of causality between vitamin D levels, PTH levels, and CKD progression. Second, the sample size may limit the generalizability of the findings, especially considering potential confounders, such as dietary habits, sunlight exposure, and comorbidities, such as diabetes. Future studies should adopt a longitudinal approach, include larger and more diverse populations, and control confounding variables.

Conclusion

The study demonstrated a statistically significant decline in 25 (OH) D and 1,25 $(OH)_2$ D levels as CKD progressed. In contrast, iPTH levels increased significantly across CKD stages. Furthermore, the 1,25 $(OH)_2$ D /iPTH decreased progressively. Clinically, these findings highlight the importance of regular monitoring of vitamin D and PTH levels in CKD patients.

List of abbreviations

ACR, albumin-to-creatinine ratio;
1–25(OH)2D 1,25 (OH)2 vitamin D;
25(OH)D:25 (OH) vitamin D;
ESKD: end-stage kidney disease;
SHPT: secondary hyperparathyroidism;
WRF: Worsening renal function;
VDR: Vitamin D Receptor;
iPTH: intact Parathyroid Hormone;
RT: Room Temperature;
eGFR: estimated glomerular filtration rate;
CKD: Chronic kidney disease.

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Authors contributions

The authors contributed equally in conceptualizing the research, collecting data, data analysis and writing-up, editing, and reviewing the manuscript.

Conflict of interest

None to declare.

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