THE ASSOCIATION BETWEEN SERUM VITAMIN D DEFICIENCY AND BONE MINERAL DENSITY IN CHRONIC KIDNEY DISEASE PATIENTS WITH REDUCED ESTIMATED GLOMERULAR FILTRATION RATE

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ABSTRACT

Background: Vitamin D deficiency is common in patients with chronic kidney disease (CKD), but its impact on bone health remains understudied. **Methods:** We collected data from CKD patients with eGFR < 60 mL/min/1.73m², including clinical information, 25-hydroxyvitamin D levels, and bone mineral density (BMD) measurements using DEXA between August 2020 and August 2021. **Results:** In a cohort of 96 patients, 63 (65.6%) were female, mean age was 62.3 ± 10.4 years, mean BMI was 22.8 ± 3.4 kg/m², and mean eGFR was 10.1 ± 7.3 ml/min. CKD staging included 13 (13.5%) in stage 3, 19 (19.8%) in stage 4, and 64 (66.7%) in stage 5, with or without dialysis. Mean serum vitamin D level was 21.3 ± 12.6 ng/ml. Hypovitaminosis D was prevalent in 74 (77.1%) cases, categorized as slight reduction in 19 (25.7%), moderate reduction in 33 (44.6%), and severe reduction in 22 (29.7%). Mean BMD at femoral neck was 0.725 ± 0.157 g/cm², and at lumbar spine, it was 0.873 ± 0.201 g/cm². Osteopenia and osteoporosis were found in 43 (44.8%) and 19 (19.8%) patients, respectively, at the femoral neck, and in 39 (40.6%) and 17 (17.7%) patients, respectively, at the lumbar spine. Statistically significant associations were observed between serum vitamin D levels and BMD at both sites: femoral neck (regression coefficient: 3.3 x 10^{-3}, coefficient of determination: 0.09) and lumbar spine (regression coefficient: 5.1 x 10^{-3}, coefficient of determination: 0.063). **Conclusion:** Vitamin D deficiency was common in CKD patients with eGFR < 60 ml/min/1.73m², and a modest but statistically significant association exists between serum vitamin D levels and BMD at both the femoral neck and lumbar spine

Keywords: *Vitamin D, bone mineral density, chronic kidney disease, reduced estimated glomerular filtration rate, eGFR.*

I. INTRODUCTION

Chronic kidney disease (CKD) affects about 10% of the population and presents a global health challenge due to its increasing prevalence, grim prognosis, and high treatment expenses [1]. Metabolic bone issues in CKD involve irregularities in calcium, phosphorus, parathyroid hormone (PTH), and vitamin D metabolism, as well as bone-related problems and extra-skeletal calcification [2]. These changes typically surface early when the estimated glomerular filtration rate (eGFR) is < 60 ml/min/1.73m^2, leading to lasting complications like osteoporosis, fractures, pain, disability, reduced quality of life, increased treatment costs, and elevated mortality rates. This condition is particularly severe given that it arises in the context of pre-existing kidney issues known as CKD [3].

Metabolic bone problems in CKD result from disturbances in the endocrine axis encompassing PTH, vitamin D, and FGF23 (Fibroblast growth factor 23) - bone - kidney interactions [2]. Vitamin D deficiency is

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notably prevalent in CKD, with deficiency rates rising as eGFR decline (40.7% in stage 3 CKD, 61.5% in stage 4, 85.7% in stage 5) [4]. Currently, there is limited research in Vietnam addressing vitamin D deficiency and its consequences on bone health in CKD patients. Thus, this study aims to determine serum vitamin D reduction rates and establish an association between serum vitamin D levels and bone density in CKD patients with an eGFR below 60 ml/min/1.73m^2.

II. MATERIAL AND METHODS

2.1. Study design and population

This single-center cross-sectional study enrolled individuals aged ≥ 18 years who had been diagnosed with CKD and had an eGFR below 60 ml/min/1.73m^2, as per the KDOQI 2012 criteria. The study was conducted at Trung Vuong Hospital in Ho Chi Minh City, Vietnam, between August 2020 and August 2021. Exclusion criteria comprised individuals with chronic medical conditions like hyperthyroidism, Cushing's syndrome, chronic liver disease, multiple myeloma, bone metastases from cancer, or those taking glucocorticoid medications. Additionally, individuals with spinal deformities that hindered accurate bone density measurement, those unable to provide medical and disease history, and pregnant women were also excluded.

2.2. Data collection. All eligible patients had their clinical and laboratory data, including serum ionized calcium, phosphorus, PTH, and 25-hydroxyvitamin D levels, collected. Bone mineral density (BMD) was assessed using DEXA (Dual Energy X-ray Absorptiometry). The Charlson comorbidity index was employed to summarize the severity of comorbidities [5].

2.3. Statistical Analysis. The data were analyzed using SPSS software, version 25. Continuous variables with a normal distribution were presented as mean ± standard deviation (M±SD), while categorical variables were presented as absolute numbers (percentages): n (%). Serum vitamin D levels and bone density were assessed for their relationship using linear regression analysis. A p-value < 0.05 was considered statistically significant.

III. RESULT

The study included 96 patients, mean age 62.3 ± 10.4 years (range: 24-83 years), 65.6% were female (Table 1). The mean body mass index (BMI) was 22.8 ± 3.4 kg/m^2 (range: 14.5-31.6 kg/m^2), and the mean Charlson comorbidity index was 6.0 ± 2.1 points (range: 2-12 points). The mean eGFR rate was 10.1 ± 7.3 ml/min/1.73m^2, and the mean duration of CKD was 5.3 ± 3.4 years (range: 1 month - 16 years). In the femoral hip, the mean BMD was 0.725 g/cm² ± 0.157, while in the lumbar spine, it was 0.873 g/cm² ± 0.201.

Table 1. ***Characteristics of the studied patients***

Variables	Number (n)	Frequency (%)
Female	63	65.6
Postmenopausal women	53	84.1
Age group		
• < 50	11	11.4
• 50 - 59	22	22.9
• 60 - 69	37	38.5

Variables	Number (n)	Frequency (%)
• ≥ 70	26	27.1
BMI		
• < 18.5	12	12.5
• ≥ 18.5	84	87.5
Charlson comorbidity index > 5 points	60	62.5
Comorbidities:		
• Hypertension	96	100
• coronary artery disease	84	87.5
• Dyslipidemia	81	84.3
• Diabetes mellitus	39	40.6
Chronic kidney disease		
• Stage 3	13	13.5
• Stage 4	19	19.8
• Stage 5 (with and/or without dialysis)	64	66.7
Kidney replacement treatments		
• Comprehensive conservative care	42	43,8
• Hemodialysis	45	46,9
• Peritoneal dialysis	09	9,4
Osteopenia		
• Hip femur	43	44,8
• Lumbar vertebrae	39	40,6
Osteoporosis		
• Hip femur	19	19,8
• Lumbar vertebrae	17	17,7

Table 2 showed serum ionized calcium, phosphorus, and PTH levels. Out of the patients, 37 (38.6%) had low serum ionized calcium (Ca++ < 1.1 mmol/L), 47 (49%) had high serum phosphorus (P > 1.45 mmol/L), and 75 (78.1%) had elevated serum PTH (PTH > 65 pg/mL).

Table 2. ***Characteristics of serum ionized calcium, phosphorus, and PTH level***

Variables	Ca ++ (mmol/l)	Phosphorus (mmol/l)	PTH (pg/ml)
Mean ± standard deviation	1.1 ± 0.1	1.5 ± 0.7	290.7 ± 424
Kidney replacement treatments			
• Comprehensive conservative care, M±SD	1.0 ± 0.1	1.6 ± 0.4	191.9 ± 136.8
• Hemodialysis, M±SD	1.2 ± 0.1	1.3 ± 0.6	248.2 ± 349.9
• Peritoneal dialysis, M±SD	1.0 ± 0.1	2.2 ± 0.8	707.9 ± 865.7

Vitamin D deficiency was found in 77.1% of patients, with a mean serum vitamin D level of 21.3 ± 12.6 ng/ml (range: 3-64.8 ng/ml) (Table 3).

Table 3. ***Characteristics of serum vitamin D levels***

Serum vitamin D levels	Number (n)	Frequency (%)
Normal (≥ 30 ng/ml)	22	22.9
Vitamin D deficiency (< 30 ng/ml)	74	77.1
• Mild (21-29.9 ng/ml)	19	25.7
• Moderate (10.1-20.9 ng/ml)	33	44.6
• Severe (≤ 10 ng/ml)	22	29.7

When analyzing serum vitamin D levels based on gender, BMI, and kidney replacement methods, significant disparities were observed in all cases ($p < 0.05$), with females having lower average vitamin D levels. Within the kidney replacement method group, the peritoneal dialysis group had the lowest mean vitamin D levels (Table 4). No statistically significant differences were found among age groups and postmenopausal status groups.

Table 4. ***Serum vitamin D level comparisons across studied subgroups***

Variables	n (%)	Vitamin D (ng/ml) M±SD	p
Age group			
• < 50	11 (11.4%)	21.5 ± 12.9	0.942
• 50 - 59	22 (22.9%)	23.4 ± 16.0	
• 60 - 69	37 (38.5%)	20.9 ± 11.1	
• ≥ 70	26 (27.1%)	20.1 ± 11.4	
Gender			
• Female	63 (66%)	19.0 ± 11.7	**0.009**
• Male	33 (34%)	26.0 ± 13.7	
Postmenopausal status			
• Yes	53 (84,1%)	18,9 ± 11,2	0.834
• No	10 (15,9%)	19,6 ± 14,7	
BMI			
• < 18,5	12 (12,5%)	29,2 ± 13,7	**0.048**
• 18.5 ≤ BMI < 23	47 (49.0%)	22.1 ± 13.8	
• 23 ≤ BMI< 25	22 (22.9%)	16.2 ± 10.0	
• BMI ≥ 25	15 (15.6%)	20.8 ± 9.4	
Kidney replacement treatments			
• Conservative care	42 (43.8%)	16.0 ± 11.2	**0.001**
• Hemodialysis	45 (46.9%)	24.4 ± 12.7	
• Peritoneal dialysis	09 (9.4%)	12.2± 8.1	

In a multivariate linear regression model that included age, male gender, BMI, serum vitamin D, serum ionized calcium, serum phosphorus, PTH, and eGFR, it was shown that serum vitamin D levels and male gender were significantly associated with BMD in the hip femur and lumbar vertebrae. The beta coefficients were $3.3x10^{-3}$ (p=0.02) and $5.1x10^{-3}$ (p=0.006), respectively, for serum vitamin D levels in the hip femur and lumbar vertebrae.

Table 5. ***Multivariate regression analysis of the association between serum vitamin D concentration and bone mineral density***

Variables	Bone density of hip femur			Lumbar vertebrae		
	β	**P**	**R^2**	**β**	**P**	**R^2**
Male	0.17	**0.0009**	0.09	0.11	**0.02**	0.063
Age	$2.4x10^{-3}$	0.11		$2.2x10^{-3}$	0.33	
BMI	0.13	0.83		$4.7x10^{-3}$	0.46	
Vitamin D	$3.3x10^{-3}$	**0.02**		$5.1x10^{-3}$	**0.006**	
Serum ionized calcium	0.13	0.22		$-1.4x10^{-4}$	0.93	
Serum phosphorus	$-1.5x10^{-2}$	0.61		$3.8x10^{-2}$	0.39	
PTH	$-4.4x10^{-5}$	0.27		$-3.4x10^{-5}$	0.55	
eGFR	$4.7x10^{-5}$	0.49		$-1.3x10^{-4}$	0.17	

IV. DISCUSSION

In this study, our aim was to assess the decline in serum vitamin D levels and investigate the relationship between these levels and bone density in CKD patients with reduced eGFR. Our findings revealed that 77.1% of the patients had insufficient vitamin D levels, which is consistent with the results reported in other studies. For instance, Rozita at al. found a 76% vitamin D deficiency rate in a group of 50 CKD patients in stages 2 to 4 [6]. Kim and co-authors conducted a study on 210 CKD patients with eGFR ranging from 10 to 59 ml/min/1.73 m^2, showing deficiency rates of 40.7% (stage 3), 61.5% (stage 4), and 85.7% (stage 5) [4]. Similarly, in a study by Satirapoj et al. involving 2,895 CKD patients in Thailand, the corresponding deficiency rates were 66.6% (stage 3a), 70.9% (stage 3b), 74.6% (stage 4), and 84.7% (stage 5) [18]. In general, these studies concluded that vitamin D deficiency is highly prevalent and associated with various stages of CKD [7].

In our study, the overall mean serum vitamin D concentration was 21.3 ± 12.6 ng/ml, with females having lower levels than males (19.0 ± 11.7 ng/ml compared to 26.0 ± 13.7 ng/ml). This trend aligns with findings from Nguyen Huu Vu Quang, where vitamin D levels in females were lower than in males in both with or without hemodialysis, although the difference was not statistically significant [8]. Similarly, in a study by Lu Cong Trung on 81 CKD patients undergoing hemodialysis, it was found that 56.8% had vitamin D deficiency, with females having lower vitamin D levels compared to males (24.7 ± 8.9 pg/ml vs. 32.3 ± 8.8 pg/ml) [9]. Additionally, factors associated with vitamin D deficiency, such as anemia, diabetes mellitus, elevated serum phosphorus, female gender, and reduced serum albumin, were consistent with findings from Rozita et al. [6].

We observed that serum vitamin D levels in the peritoneal dialysis group (12.2 ± 8.1 ng/ml) were significantly lower than in the hemodialysis group (24.4 ± 12.7 ng/ml) and the conservative treatment group (16.0 ± 11.2 ng/ml) ($p < 0.05$). A cross-sectional study of peritoneal dialysis patients in Saudi Arabia reported similar mean serum vitamin D levels to those in our peritoneal dialysis group [10]. Most peritoneal dialysis patients are at high risk for vitamin D deficiency due to the loss of 25(OH) vitamin D, the precursor of active vitamin D, during the peritoneal dialysis process. Other contributing factors include CKD, nutritional deficits from dietary restrictions, and reduced exposure to sunlight [10].

In our linear regression analysis, we found a weak association between serum vitamin D levels and bone density, which aligns with the study conducted by Michelle Denburg et al., who investigated bone density and mineral disorders in 171 children and adults aged 5-21 with CKD stages 2-5D [11]. The study revealed a positive correlation between independent factors and bone density, including low blood calcium levels and low 25(OH) vitamin D levels, as well as a negative correlation with high blood $1,25(OH)_2$ vitamin D levels and high PTH levels [11]. In addition to the pediatric and young adult population studied by Denburg and colleagues, Lee Yong Ho et al. discovered an association between low serum vitamin D and decreased bone density in a group of older patients, both with and without mild to moderate CKD, across both genders. CKD patients with vitamin D deficiency had significantly lower bone

density at the femoral neck and hip compared to those with normal kidney function and adequate vitamin D levels, irrespective of gender. Linear regression analysis at the femoral neck showed determination coefficients of r = 0.120 for males and r = 0.136 for females, while at the hip, determination coefficients were r = 0.120 for males and r = 0.122 for females [12]. The authors concluded that older CKD patients with mild to moderate kidney disease and vitamin D deficiency had significantly lower BMD values at the femoral neck and hip compared to the general population [12].

In a cross-sectional study involving 69 hemodialysis patients by Mucsi et al., results showed that 59% of the patients had vitamin D levels below 20 nmol/l. Vitamin D had a positive correlation with bone density measured by DEXA in hemodialysis patients ($r = 0.424$, $p < 0.01$) and was independently correlated with decreased bone density measured by quantitative ultrasound ($\beta = 0.262$, $p < 0.05$) [13]. The authors concluded that vitamin D deficiency may contribute to the weakening of bone strength in hemodialysis patients. A study in 2020 by Maimun Syukri et al. also demonstrated a correlation between the hemodialysis process, vitamin D levels, and bone density [19]. Valkovsky et al. reported similar results, with a 96% deficiency rate in 25(OH) vitamin D and reduced bone density in hemodialysis patients [14]. Coen et al. observed 104 hemodialysis patients who underwent pelvic bone biopsy, and the results indicated that patients with vitamin D deficiency had lower mineralization levels and bone formation rates, regardless of $1,25(OH)_2$ vitamin D and PTH levels [15].

Our study has several limitations. Firstly, its cross-sectional design restricts us from establishing a definitive causal relationship between vitamin D deficiency and bone density in chronic kidney disease. Secondly, the small sample size in our study may impede the identification of associations between bone density and other factors. Furthermore, larger studies with expanded sample sizes are needed to assess the effectiveness of vitamin D supplementation and exercise programs in preventing muscle mass and bone loss. This is particularly crucial for early-stage CKD patients and younger individuals, as restoring lost muscle mass in older individuals may pose challenges.

V. CONCLUSION

In summary, this study revealed that 77.1% of CKD patients with eGFR below 60 ml/min/1.73m² had serum vitamin D deficiency. Additionally, a statistically significant but modest association was observed between serum vitamin D levels and bone density at the hip femur and lumbar vertebrae sites in these patients.

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