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Original Research Article

Association Between Serum Vitamin D and Hepcidin Serum Levels in Children with Chronic Kidney Disease: A Cross-Sectional Study

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Abstract

Background: Chronic kidney disease (CKD) is a major health issue that frequently associated with anemia and poor outcome. Hepcidin, the primary regulator of systemic iron homeostasis, is typically elevated in CKD, thereby exacerbating erythropoietic dysfunction. Emerging evidence indicates that vitamin D may modulate anemia through anti-inflammatory pathways and the stimulation of erythropoiesis. However, the specific interplay between hepcidin and vitamin D in pediatric CKD populations remains insufficiently characterized.

Objective: This study aimed to evaluate the correlation between serum hepcidin and vitamin D concentrations in children diagnosed with CKD.

Methods: A cross-sectional study was conducted involving 40 pediatric patients (aged 3 months to <18 years) recruited via consecutive sampling. Serum hepcidin and vitamin D levels were quantified using Enzyme-Linked Immunosorbent Assay (ELISA). Statistical correlations were analyzed to determine the relationship between these two parameters.

Results: Mean serum hepcidin levels demonstrated significant variance across different vitamin D status cohorts ($p < 0.001$). Based on the Spearman Correlation test, A robust negative correlation was observed between serum hepcidin and vitamin D levels ($r = -0.856$, $p < 0.001$), indicating that lower vitamin D concentrations are significantly associated with elevated hepcidin levels.

Conclusion: Serum hepcidin levels are inversely correlated with vitamin D concentrations in pediatric CKD patients. These findings suggest that vitamin D deficiency may play a role in upregulating hepcidin production, potentially clinical worsening of anemia in this population.

Keywords: *Hepcidin; Vitamin D; Chronic Kidney Disease; Anemia; Children*

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INTRODUCTION

Chronic kidney disease (CKD) represents a critical pediatric health challenge, characterized by rising prevalence and mortality rates globally.^{1, 2} Anemia is a ubiquitous complication of CKD, affecting approximately 15% of the total CKD population-nearly 5 million patients in the United States alone. Hepcidin, an antimicrobial peptide hormone, serves as the primary regulator of iron homeostasis by blocking intestinal iron absorption and inhibiting iron efflux from macrophages and hepatocytes.³ Pathologically elevated hepcidin levels further sequester iron within

the reticuloendothelial system, restricting iron bioavailability for erythropoiesis and hemoglobin synthesis.⁴

Recent studies indicates that vitamin D modulates hepcidin synthesis by directly inhibiting its transcriptional expression. In vitro studies have further demonstrated that vitamin D downregulates both pro-inflammatory cytokines and serum hepcidin.^{3, 5} Patients with CKD are particularly susceptible to 25(OH)D

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deficiency due to restricted dietary intake, inadequate sun exposure, uremia-induced impairment of vitamin D photoconversion, and significant vitamin D loss through proteinuria.⁶⁻⁸ Beyond its role in mineral and bone disorders, vitamin D is increasingly recognized for its impact on anemia in CKD.^{2,7}

While several studies have established a correlation between serum vitamin D and hepcidin in adult CKD cohorts, data regarding this relationship in pediatric patients—specifically within the Indonesian population—remain sparse. Therefore, this study aims to evaluate the correlation between serum vitamin D and hepcidin levels in children with CKD.

MATERIALS AND METHODS

Study design and participants

This cross-sectional study was conducted at Hasanuddin University Hospital and Dr. Wahidin Sudirohusodo Hospital in Makassar. The study protocol was approved by the Institutional Review Board, and written informed consent was obtained from the parents or legal guardians of all participants.

A total of 40 pediatric patients (aged 3 months to <18 years) diagnosed with CKD were enrolled via consecutive sampling. CKD was defined according to the KDIGO guidelines as a glomerular filtration rate (GFR) <60 mL/min/1.73 m² and/or evidence of persistent proteinuria. Exclusion criteria

included a history of malignancy, impaired hepatic function, or current vitamin D supplementation.

Measurement of Serum Vitamin D and Hepcidin

Serum vitamin D levels were measured using Enzyme-Linked Immunosorbent Assay (ELISA) kits (DBC Canada Inc.). Vitamin D status was categorized into three groups: deficiency (<20 ng/mL), insufficiency (21–29 ng/mL), and sufficiency (≥30 ng/mL). Serum hepcidin concentrations were recorded in ng/mL.

Statistical analysis

Data were analyzed using Microsoft Excel 2013 and SPSS version 20 (IBM Corp., Armonk, NY). The normality of continuous variables was assessed using the Shapiro-Wilk test. Inter-group comparisons were performed using the unpaired Student's t-test for normally distributed data and the Mann-Whitney U test for non-normally distributed data. Correlation between variables was evaluated using Pearson's correlation coefficient for parametric data and Spearman's rank correlation for non-parametric data. Statistical significance was defined as $p < 0.05$.

RESULTS

This study included 40 pediatric patients with chronic kidney disease (CKD). Nearly half were older than 12 years, with an equal distribution of males and females. Vitamin D deficiency was highly prevalent (70%), with a mean serum 25(OH)D level of $20.69 \pm$

Table 1. Characteristics of study participants

Characteristics	N (%)	Median (Min-Max)
Age (Month)		136.50 (7-215)
0 – 5 years	7 (17.5%)	
>5 – 12 years	14 (35.0%)	
>12 years	19 (47.5%)	
Sex		
Male	20 (50.0%)	
Female	20 (50.0%)	
Vitamin D (25OHD) (ng/mL)		15.65 (5.26-65.10)
Deficiency	28 (70.0%)	14.50 (5.26-22.60)
Insufficiency	5 (12.5%)	20.70 (19.60-32.60)
Sufficiency	7 (17.5%)	39.80 (22.30-65.10)
Hepcidin (ng/mL)		26.30 (15.80-36.30)
GFR (ml/min/1.73 m²)		85.20 (3.00-374.00)
Stage		
1	20 (50.0%)	
2	4 (10.0%)	
3a	2 (5.0%)	
3b	1 (2.5%)	
4	2 (5.0%)	
5	11 (27.5%)	
TOTAL	40 (100.0%)	

Table 2. Correlation between hepcidin levels and vitamin d levels in children with CKD

Variable	Vitamin D (25(OH)D) (ng/mL)	
	r	p
Hepcidin (ng/mL)	-0.856	*<0.001

*Spearman Correlation test

13.06 ng/mL, while only 17.5% had sufficient levels. The mean hepcidin level was 26.59 ± 4.80 ng/mL, and the median glomerular filtration rate (GFR) was 85.20 mL/min/1.73 m², indicating variability within the group (Table 1).

Post hoc analysis demonstrated significant differences in mean hepcidin levels between the vitamin D deficiency and insufficiency groups ($p < 0.001$) and between the deficiency and sufficiency groups ($p = 0.001$). No significant difference was observed between the insufficiency and sufficiency groups ($p = 0.123$) (Figure 1).

Spearman correlation analysis showed a significant negative correlation between hepcidin and vitamin D levels ($p < 0.05$), indicating that higher hepcidin levels were associated with lower vitamin D concentrations (Table 2). Most subjects were clustered in the vitamin D deficiency group, whereas the lowest hepcidin levels were observed in individuals with vitamin D levels ≥ 30 ng/mL (sufficiency category) (Figure 2).

DISCUSSION

Chronic kidney disease (CKD) represents an increasing global health burden, yet epidemiological data remain limited in many regions, including Indonesia. National surveillance (Riskesdas 2018) reported a higher prevalence of CKD in males within the 15–24-year age group (0.13%).⁹ In the present study, CKD was most frequent in children older than 12 years, a finding consistent with reports from previous studies which described higher prevalence in older pediatric age groups across multiple countries.^{10–13} However, a study by Hidayati et al.¹⁴ reported a higher prevalence among children aged 0–5 years, highlighting geographic and population heterogeneity in pediatric CKD distribution. Unlike several prior studies that reported a modest male predominance (male:female ratios 1.2–2.0),^{10, 11, 14, 15} our study showed no significant sex difference.

Hepcidin, a hepatic acute-phase peptide, is a principal regulator of systemic iron homeostasis that restricts intestinal iron absorption and iron release from hepatocytes and macrophages; its expression is upregulated by chronic inflammation. In CKD, sustained inflammatory signaling elevates hepcidin levels, thereby limiting iron availability for erythropoiesis and contributing to anemia of chronic disease.¹⁶

We observed a strong inverse relationship between serum hepcidin and 25-hydroxyvitamin D concentrations. This result corroborates prior clinical studies reporting negative correlations between vitamin D status and hepcidin levels in CKD and dialysis populations.^{17, 18}

Mechanistically, vitamin D deficiency may promote proinflammatory cytokine production by immune cells, including those of the reticuloendothelial system, which in turn stimulates hepcidin synthesis and functional iron deficiency.^{17, 19} In addition, active vitamin D metabolites directly suppress hepcidin mRNA transcription via the vitamin D receptor in hepatocytes and monocytes, and in vitro treatment with

25(OH)D or 1.25(OH)₂D has been shown to reduce hepcidin expression.²⁰

Furthermore, 25(OH)D appears to modulate the hepcidin–ferroportin axis and intracellular iron trafficking, thereby influencing erythropoiesis and anemia pathophysiology.^{21, 22} Clinically, vitamin D supplementation has been associated with improved anemia parameters and reduced erythropoiesis-stimulating agent resistance in CKD patients, effects attributed both to direct stimulation of erythroid progenitors and to modulation of inflammation and iron handling.^{17, 19}

Taken together, our findings support a biologically plausible link between vitamin D deficiency and elevated hepcidin in pediatric CKD. These data underscore the potential of vitamin D-targeted strategies to ameliorate iron-restricted erythropoiesis; however, prospective studies are required to establish causality, define mechanisms in children specifically, and determine optimal supplementation regimens.

CONCLUSION

In this study, serum hepcidin levels were found to be inversely correlated with vitamin D concentrations in children with CKD. It is suggested that vitamin D deficiency may contribute to increased hepcidin production, potentially exacerbating the severity of anemia. These findings underscore the necessity for further research to determine whether vitamin D supplementation can effectively modulate hepcidin levels and improve clinical outcomes in the pediatric CKD population.

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