Original Article

Vitamin D Insufficiency with Elevated ADMA and hs-CRP: A Single-center Study of Chronic Kidney Disease Patients Undergoing Hemodialysis

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ABSTRACT

Background: Vitamin D deficiency is a common issue among patients with chronic kidney disease (CKD) due to its ability to convert vitamin D into the active form of calcitriol, which is crucial for controlling cell inflammation. Low vitamin D levels are associated with increased inflammation and higher levels of biomarkers such as c-reactive protein and asymmetric dimethylarginine as an endogenous inhibitor of nitric oxide synthase. Those two combined become a specific marker for cardiovascular diseases, which become one of the common causes of CKD mortality.
Objective: This study examines the correlation between vitamin D insufficiency, elevated high-sensitivity c-reactive protein, and asymmetric dimethylarginine in CKD patients receiving hemodialysis.
Methods: This study used a cross-sectional design of CKD patients receiving hemodialysis in Dr. Kariadi Central General Hospital, Semarang, Indonesia, in November 2021. Thirty-six patients were randomly enrolled after meeting inclusion and exclusion criteria. Primary outcomes of Vitamin D, hs-CRP, and ADMA were measured from patients' blood after hemodialysis. A statistical analysis of Pearson's correlation was used for primary outcomes.
Results: No significant difference was found in the patient's baseline characteristics. A significant correlation between vitamin D and ADMA has been found; however, no correlation between vitamin D and hs-CRP has been found.
Conclusion: Vitamin D deficiency is correlated with elevated ADMA, indicative of endothelial dysfunction.
Keywords: chronic kidney disease, vitamin D, c-reactive protein, asymmetric dimethylarginine, cardiovascular disease.

Introduction

Chronic kidney disease (CKD) is a growing public health issue.[1] It is estimated that approximately 37 million adults in the United States are affected by this condition. At the same time, Indonesia's prevalence of CKD has continued to rise, with 4 out of 1000 people diagnosed with CKD every year.[2, 3] As a progressive loss of kidney function, CKD often requires long-term and complex medical management, including strict dietary regimens, various medications, and, ultimately, renal replacement therapies like dialysis or transplantation.[4] Cardiovascular disease stands

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out as a leading contributor to increased morbidity and mortality in CKD.[5] This is attributable to the complex interplay between renal impairment and pathological processes such as hypertension, dyslipidemia, and chronic inflammation, which are common in CKD and predispose patients to atherosclerosis and heart failure.[6-8] Additionally, CKD often leads to alterations in mineral metabolism and anemia, further exacerbating cardiac stress.[9, 10]

Vitamin D deficiency is a common and clinically significant issue among patients with CKD.[11] The kidneys play an essential role in converting vitamin D to its active form, calcitriol, which is crucial for controlling the expression of genes that regulate cell inflammation and proliferation.[12] A significant decrease in renal function impairs this conversion process, often leading to vitamin D insufficiency or deficiency in individuals with CKD.[11] Furthermore, Vitamin D is crucial in cardiovascular health, regulating blood pressure, maintaining endothelial function, and preventing arterial stiffness.[13-15] Low vitamin D levels are linked to higher inflammation and elevated biomarkers, such as C-reactive protein, indicating an increased risk for CKD.[16]

Asymmetric dimethylarginine (ADMA) is an endogenous inhibitor of nitric oxide (NO) synthase, and its accumulation is a well-established marker of cardiovascular risk and endothelial dysfunction in patients with CKD.[17, 18] Elevated levels of ADMA can lead to impaired nitric oxide production, which can result in increased arterial stiffness, endothelial dysfunction, hypertension, and ultimately contribute to cardiovascular diseases.[17] Studies have explored the potential links between these biomarkers and the development of cardiovascular complications in CKD patients, identifying them as potential therapeutic targets to reduce cardiovascular risk.[19, 20]

However, the relationship between vitamin D status, inflammation, and cardiovascular outcomes in CKD patients undergoing hemodialysis remains an ongoing investigation. We hypothesize that vitamin D levels were correlated with systemic inflammatory and endothelial dysfunction, depicted by high-sensitivity C-reactive protein (hs-CRP) and ADMA levels, respectively. This study aims to investigate the correlation between vitamin D insufficiency, elevated hs-CRP as a marker of systemic inflammation, and ADMA as a marker of endothelial dysfunction in a CKD patient receiving hemodialysis at a single-center hospital in Semarang.

Methods

Design and participants

This study employed a cross-sectional design to examine the association between vitamin D status and hs-CRP levels in CKD patients undergoing hemodialysis at Dr. Kariadi Central General Hospital, Semarang, Indonesia, starting in November 2021. The Ethics Committee of Dr. Kariadi Central General Hospital approved this study. The study population consisted of adult CKD patients receiving maintenance hemodialysis at the Nephrology Outpatient Clinic of Dr. Kariadi Central General Hospital during the study period. To be included, patients must be 18 years or older, have a normal body mass index, have been on hemodialysis for at least 3 months, and have provided written informed consent. Exclusion criteria are a history of parathyroidectomy, malignancy, severe liver disease, or if they were taking vitamin D supplements or medications that could significantly impact vitamin D and inflammatory status. A minimum sample of 29 patients was randomly selected to participate in the study.

Outcomes

Primary outcomes

The primary outcomes were serum 25-hydroxyvitamin D (25D) levels and high-sensitivity C-reactive protein (hs-CRP) levels, high-sensitivity C-reactive protein (hs-CRP) and Asymmetric Dimethylarginine (ADMA) levels in the study population. All measurements were conducted using Enzyme-linked immunosorbent assay (ELISA) with blood samples collected from the venous line before the dialysis session.

Vitamin D deficiency was defined as serum 25(OH)D levels <20 ng/mL, insufficiency as 20-30 ng/mL, and sufficiency as >30 ng/mL. High-sensitivity C-reactive protein (hs-CRP) levels >3 mg/L were considered elevated, indicating increased systemic inflammation. ADMA levels >100 ng/mL were considered elevated.

Secondary outcomes

The study also collected baseline clinical and demographic data from the patients, including age, gender, duration of hemodialysis, presence of diabetes, hypertension, and other comorbidities. Hemoglobin was obtained from medical records to assess anemia status.

Statistical analysis

Descriptive statistics were employed to characterize the study population. The relationship between vitamin D status, hs-CRP, and ADMA was assessed using Pearson's correlation coefficient. One-way ANOVA was applied to compare mean hs-CRP levels across different vitamin D status groups. A p-value of <0.05 was considered statistically significant. All analyses were performed using SPSS version 24 (IBM Corp.).

Results

The final analysis included a total of 36 CKD patients undergoing hemodialysis. These patients were all enrolled at the Nephrology Outpatient Clinic of Dr. Kariadi Central General Hospital. Of all the patients, the majority were male (55%), and the mean age was 49.11 + 11.86 years old. The average duration of hemodialysis was 21.17 + 17.84 months. Most of the patients have hypertension as a comorbidity (97%). The homogeneity test showed no significant difference (P>0.05) in the clinical characteristics (Table 1).

Table 1. Characteristics of samples from chronic kidney disease patients undergoing hemodialysis in Dr. Kariadi Central General Hospital, Semarang, Indonesia

Characteristics	n (%)	P
Sex		
Male	20 (55)	0.254
Female	16(45)	
Diabetes Mellitus		
Yes	7 (19)	0.161
No	29 (81)	
Hypertension		
Yes	35 (97)	0.167
No	1 (3)	
Use of Angiotensin drugs (ACE-I or ARB)		
Yes	33 (91)	
No	3 (9)	0.079
	Mean	
Age	49.11 ± 11.86	0.225
Haemoglobin	9.08 ± 1.06	0.586
Duration of Haemodialysis (month)	21.17 ± 17.84	0.317
Vitamin D	19.64 ± 8.04	0.704
hs-CRP	14.38 ± 26.55	0.613
BMI	23.54 ± 2.94	0.623
ADMA	105.44 ± 17.48	0.635

The mean serum 25-hydroxyvitamin D level was 20.66 + 11. ng/mL, with 22 patients (61%) having vitamin D deficiency (<20 ng/mL), 9 patients (25%) having vitamin D insufficiency, and 5 patients (14%) having sufficient vitamin D levels. The mean hs-CRP level was 14.38 + 26.55

mg/L, with 23 patients (64%) having elevated levels. The mean ADMA level was 105.44 + 17.48 ng/mL, with 24 patients (67%) having elevated levels.

Pearson's correlation analysis showed a significant negative correlation between serum 25-hydroxyvitamin D levels and ADMA (r = -0.359, p = 0.032). However, there was no significant correlation between 25(OH)D and hs-CRP levels (r = -0.202, p = 0.236), even though a negative correlation trend was shown on the scatter plot (Figure 1). A significant correlation has been shown in ADMA levels, however no correlation found in hs-CRP levels.

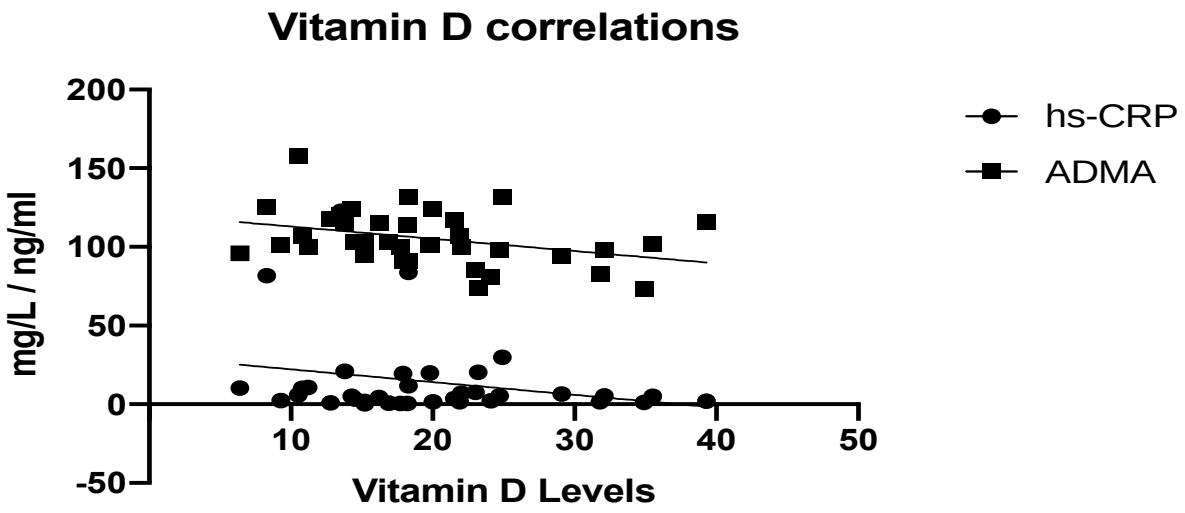

Figure 1. The correlations between vitamin D levels and hs-CRP and ADMA

One-way ANOVA analysis revealed no significant difference in mean hs-CRP levels among the different vitamin D status groups (P=0.497).

Analysis of clinical characteristics indicated that patients with diabetes and hypertension did not have significantly higher mean ADMA levels than those without these comorbidities (P=0.097 and 0.587, respectively), meaning that comorbidities were not involved in the ADMA levels. Hemoglobin levels were also not correlated with ADMA levels (P=0.426) (Figure 2).

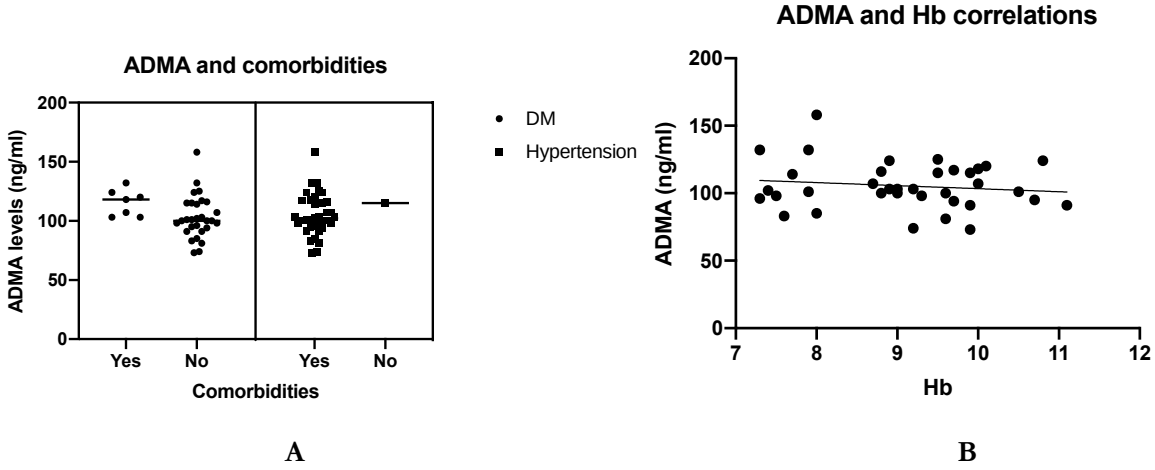

Figure 2. Correlations between confounding factors that may affect ADMA levels

2A shows correlations between ADMA and confounding factors that mostly impact endothelial dysfunction. No significant correlation was found between those two factors with ADMA levels. Figure 2B shows no correlation between ADMA levels and hemoglobin, which may also interfere with endothelial dysfunction.

Discussion

Vitamin D insufficiency is a prevalent complication in CKD patients due to their kidneys' ability to convert vitamin D into calcitriol, its active form.[12] However, in CKD, diminished kidney function hinders this process, often leading to insufficient levels of active vitamin D.[19] Vitamin D also possesses anti-inflammatory properties and contributes to maintaining endothelial function and regulating blood pressure.[16] Thus, in CKD patients, vitamin D deficiency poses a threat to elevate the risk of cardiovascular complications, which already constitute a leading cause of mortality in this patient group.

To counter these issues, CKD management often involves monitoring vitamin D levels, dietary modifications, and possibly supplementation to maintain sufficient vitamin D status and mitigate its associated risks.[11] Recognizing the multifaceted implications of vitamin D deficiency in CKD is vital, extending beyond bone health to cardiovascular risk and overall quality of life.[4]

Vitamin D deficiency in CKD patients can significantly impact inflammation levels, as hs-CRP measurements indicate.[21] Vitamin D is thought to possess anti-inflammatory properties; therefore, insufficient levels may fail to exert a normal regulatory influence on the immune system, potentially resulting in an increased inflammatory response.[22] When vitamin D levels are low, pro-inflammatory cytokines and other inflammatory mediators may be upregulated in the body.[23] This inflammatory state is measurable by hs-CRP, a sensitive marker of systemic inflammation and a predictor of cardiovascular disease risk.[24-26] Elevated levels of hs-CRP have been associated with a higher risk of cardiovascular events, particularly in CKD patients, who are already at heightened risk for cardiovascular disease.

The impact of the interplay between vitamin D deficiency and elevated hs-CRP is thus two-fold. Firstly, it may accelerate the progression of cardiovascular complications, which are a significant cause of morbidity and mortality in CKD patients.[27] Secondly, persistent inflammation can further damage kidney tissue, exacerbating the decline in renal function and potentially accelerating the progression toward end-stage renal disease.[28] While ADMA has been established as a marker of endothelial dysfunction and a predictor of cardiovascular risk in CKD, the specific relationship between vitamin D status and ADMA levels remains less clear.[17, 18]

Our first outcome shows no significant correlation between vitamin D status and hs-CRP levels in our study of CKD patients. However, we may see a suggesting trend that as vitamin D levels increase, hs-CRP levels tend to decrease, though the relationship is not statistically significant. This might be attributed to the relatively small sample size and the complex interplay of various factors affecting the vitamin D-inflammation relationship in CKD. Further research is necessary to explore the nuances of this association and the potential therapeutic implications of vitamin D supplementation for mitigating inflammation in CKD patients.[23]

Another primary outcome highlights the inverse correlation between CKD patients' vitamin D status and ADMA levels. This also aligns with previous studies that revealed a similar inverse relationship between vitamin D and ADMA in various populations.[29] However, the secondary outcome showed no correlations between comorbidities factors and ADMA levels, even though the scatterplot showed that hypertension may affect ADMA levels. An analysis of systole levels and ADMA levels may be helpful to explain the correlation. This result highlighted that the increase in ADMA is strongly

suggested to come from lower Vitamin D levels and neglected all confounding factors.

One potential mechanism by which vitamin D may exert a protective effect on endothelial function is its ability to modulate NO synthesis.[30] Vitamin D has been shown to upregulate the expression of endothelial nitric oxide synthase (eNOS), the enzyme responsible for producing nitric oxide. This critical vasodilator helps maintain vascular tone and endothelial integrity.[31, 32] Vitamin D has been demonstrated to possess anti-inflammatory properties, and its deficiency has been associated with increased oxidative stress and vascular inflammation.[33] These factors can contribute to the accumulation of ADMA, an endogenous inhibitor of nitric oxide synthase, ultimately impairing endothelial function and promoting the development of cardiovascular diseases.[34]

Conclusion

In conclusion, our findings suggest that vitamin D deficiency is associated with elevated ADMA, indicative of endothelial dysfunction, in CKD patients on maintenance hemodialysis. This has implications for the management of CKD, as addressing vitamin D deficiency may be a potential approach to mitigate inflammation-related cardiovascular risks in this high-risk patient population. However, further research is necessary to better understand the complex interplay between vitamin D, inflammation, and cardiovascular outcomes in CKD.

Limitations of the Study

The limitations of this study include its relatively small sample size and cross-sectional design, which preclude any inference of causality. This warrants larger, longitudinal investigations to better characterize the relationships between vitamin D status, inflammation, endothelial function, and other metabolic parameters in the CKD population. Furthermore, an analysis of confounding factors that may alter vitamin D levels externally is needed, such as direct sun exposure, skin type and disorder, and vitamin D absorption disturbance.

Declarations

Ethics approval and consent to participate

The Ethics Committee of Dr. Kariadi Central General Hospital approved this study and the participants have provided written informed consent.

Competing interests

There are no conflicts of interest in writing this article. This article is written neutrally with actual results.

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Author's Contribution

Idea/concept: LL. Design: LL, DLP, SC, AA, AN. Control/supervision: LL, DLP, SC, AA, AN. Data collection/processing: LL, DLP, SC, AA, AN. Analysis/interpretation: LL, DLP, SC, AA, AN. Literature review: LL, DLP, SC, AA, AN. Writing the article: FRM. Critical review: LL. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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