Reports of Biochemistry & Molecular Biology
Vol.12, No.3, Oct 2023

Original article

www.RBMB.net

The Role of Vitamin D Binding Protein and Vitamin D Level in Mortality of Sepsis Patients

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Abstract

Background: Vitamin D plays crucial roles in immune cell function, including macrophage activation, immune response modulation, and antimicrobial peptide production. Low vitamin D levels can result in reduced immune response, heightened inflammation, and impaired organ function, thereby exacerbating sepsis severity and impacting patient prognosis. This study investigates the influence of vitamin D binding protein expression and vitamin D levels on the mortality of septic patients.

Methods: This analytical observational study employs a case-control approach and involves patients at the Critical Care Unit of Dr. M. Djamil General Hospital in Padang, Indonesia. The study comprises 40 patients in the case group and 40 patients in the control group. Vitamin D and vitamin D binding protein levels are assessed using the enzyme-linked immunosorbent assay method.

Results: Vitamin D and vitamin D binding protein levels were observed to be lower in the case group compared to the control group. In the case group, the majority of patients had vitamin D binding protein levels below 200 µg/mL. A significant association was found between vitamin D levels and mortality in sepsis patients ($P< 0.05$). Patients with vitamin D levels below 20 µg/mL faced a 2.54 times higher risk of mortality than those with levels exceeding 20 µg/mL.

Conclusions: Diminished levels of vitamin D binding protein and vitamin D contribute to an increased risk of mortality in septic patients.

Keywords: Antiinflammation, Mortality, Sepsis, Vitamin D Binding Protein, Vitamin D level.

Introduction

Sepsis is a severe condition in which the body's response to infection causes widespread inflammation (1), potentially resulting in life-threatening organ dysfunction (1, 2). A critical aspect of sepsis involves the role of vitamin D and vitamin D binding protein (VDBP) in regulating the body's immune response (3). Vitamin D deficiency has been linked to an increased risk of infection and inflammation (4, 5). Additionally, several studies have shown that low vitamin D levels may be associated with the worsening of sepsis and adverse outcomes in septic patients (6-8).

Vitamin D binding protein (VDBL) is a critical protein responsible for transporting and regulating vitamin D levels in humans (9). It binds to vitamin D in the blood and facilitates its delivery to body tissues. Furthermore, VDBP plays a multifaceted immunomodulatory role in regulating inflammatory and immune responses (10).

Vitamin D possesses anti-inflammatory

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Received: 25 Jul, 2023; Accepted: 15 Sep, 2023

[DOI: 10.61186/rbmb.12.3.366]

properties and can influence the inflammatory response to infection (11). Low vitamin D levels can disrupt the proper regulation of inflammation, potentially exacerbating inflammation in septic patients. Vitamin D is known to have essential roles in immune cell function, including macrophage activation, immune response modulation, and antimicrobial peptide production (12). Low vitamin D levels can hinder immune cell function and impact the body's ability to combat infection in septic patients (13).

VDBP has a multifaceted immunomodulatory role beyond its function as a vitamin D binder (10). Multiple studies have indicated that VDBP can interact with other immune system components and affect the activity of immune cells, such as T-cells and dendritic cells (11, 14, 15). VDBP can interact with T-cell receptors, including the receptor for T-cell receptor (TCR) activation and the interleukin-2 receptor (IL-2R). This interaction can influence intracellular signaling pathways, regulating T-cell activation, proliferation, and differentiation. VDBP can impact T-cell proliferation, namely the ability of T-cells to proliferate and increase in number (16). Additionally, VDBP can influence T-cell differentiation, particularly in the transformation of T-cells into various subpopulations with specific functions. T cells produce multiple cytokines that play a role in cellular communication and the regulation of immune responses (15, 16). Prior studies have demonstrated that VDBP can modulate cytokine production by T cells, affecting both pro-inflammatory and anti-inflammatory cytokines (7, 17). This modulation can influence the immune response and inflammation associated with sepsis.

Low VDBP levels can significantly predict a poor prognosis in septic patients (9) and is associated with more severe inflammation and an imbalanced immune response in sepsis (9-11). Low vitamin D levels can lead to a reduced immune response, increased inflammation, and diminished organ function, potentially worsening sepsis severity and impacting patient prognosis (10. 14). This study aims to explore the role of VDBP expression and vitamin D levels in the mortality of septic patients.

Materials and Methods

Ethics statement

This study was carried out in accordance with the Helsinki Declaration's ethical principles for human clinical research (18). The Ethics Committee of Dr. M. Djamil Hospital, Padang, Indonesia, also approved the research protocol (approval no. LB.02.02/5.7/393/2022). In addition, participants or their legal guardians were informed about the study's objective and provided informed consent to participate.

Subjects

This study follows an analytic observational design with a case-control approach. The study subjects consisted of patients at the Critical Care Unit of Dr. M. Djamil General Hospital in Padang, Indonesia, who met specific inclusion criteria. A total of 40 patients were included in both the case and control groups, with the patients in these groups matched for age and gender.

The inclusion criteria for the case group were as follows: (1) patients with sepsis caused by microorganisms, (2) aged between 18 and 85 years, (3) procalcitonin levels ≥ 2 μg/mL, (4) lactate levels ≥ 1.6 mmol/L, (5) an Acute Physiology and Chronic Health Evaluation (APACHE) II score ≥ 10. (6) a quick Sepsis-related Organ Failure Assessment (qSOFA) score ≥ 2, and (7) patients who passed away within 30 days from the commencement of the observation period.

On the other hand, the inclusion criteria for the control group were: (1) patients with sepsis caused by microorganisms, (2) aged between 18 and 85 years, (3) procalcitonin levels ≥ 2 μg/mL, (4) lactate levels ≥ 1.6 mmol/L, (5) an APACHE II score greater than 10. (6) a qSOFA score ≥ 2, and (7) patients who survived beyond 30 days from the start of the observation period.

The exclusion criteria encompassed patients with sepsis attributed to Mycobacterium tuberculosis, viral, fungal, and

[DOI: 10.61186/rbmb.12.3.366]

parasite infections, as well as patients who had received vitamin D supplementation.

Biochemical analysis

Vitamin D levels and vitamin D-binding protein (VDBP) levels were assessed using the enzyme-linked immunosorbent assay (ELISA) method. Vitamin D levels below 20 mg/mL indicated vitamin D deficiency, while VDBP levels below 200 µg/mL indicated VDBP deficiency. In accordance with the manufacturer's instructions (R&D Systems®, Minneapolis, USA), 50 µl of standard diluent or serum samples were added to each well and incubated at 37 °C for 30 minutes. After washing the plates, 100 µl of the biotinylated antibody solution (Boster, California, USA) was added and incubated for 30 minutes at 37 °C. Following three washes, 50 µl of the avidin-peroxidase complex solution (Boster, California, USA) was added and incubated for 15 minutes at 37 °C. After another wash, 50 µl of tetramethylbenzidine color solution (Sigma-Aldrich, Germany) was added and kept in the dark for 15 minutes at 37 °C. Finally, 50 µl of stop solution was added to terminate the reaction. The absorbance was measured at 450 nm using an ELISA reader (BioTek Epoch, Winooski, VT, USA).

Statistical Analysis

Statistical analysis was conducted using SPSS Statistics 25.0 Software (SPSS Inc., Chicago, Illinois, USA). All descriptive and quantitative data were expressed as percentages and as the mean ± standard deviation (SD), respectively. Bivariate analysis was performed to determine the relationship between VDBP and vitamin D levels and mortality in sepsis patients, utilizing the chi-square test. P-values less than 0.05 were considered statistically significant.

Results

Table 1 displays the baseline characteristics of the study subjects. It is evident from Table 1 that there were no significant differences in age and gender between patients in the case and control groups. The majority of patients in both groups were overweight. Various comorbid diseases, including diabetes mellitus, chronic kidney disease, cardiovascular disorders, and chronic obstructive pulmonary disorder, were present in all groups. No significant differences in APACHE II and qSOFA scores were observed between the case and control groups.

Table 1. Baseline characteristics of patients.

Characteristics (mean±SD)	Groups		p-value
	Case	Control	
Age (years)	51.8±4,5	51.2±4.8	0.121
Gender			
Male	16 (40%)	16 (40%)	1.000
Female	24 (60%)	24 (60%)	
Body mass index			
Underweight	3 (7.5%)	2 (5%)	0.564
Normoweight	14 (35%)	15 (37.5%)	
Overweight	23 (57.5%)	23 (57.5%)	
Diabetes mellitus	4 (10%)	3 (7.5%)	0.675
Chronic kidney injury	5 (12.5%)	4 (10%)	0.567
Cardiovascular disorder	4 (10%)	3 (7.5%)	0.664
COPD	2 (5%)	2 (5%)	1.000
APACHE II Score (mean±SD)	20.4±1.3	20.9±1.4	0.878
qSOFA score (mean±SD)	7.1±0.2	6.6±0.3	0.767

Notes: APACHE II (The Acute Physiology and Chronic Health Evaluation; COPD: chronic obstructive pulmonary disorder; SD: standard deviation; qSOFA: quick Sepsis related Organ Failure Assessment.

[DOI: 10.61186/rbmb.12.3.366]

Table 2 presents a comparison of the laboratory evaluations between the two groups. The results of routine blood tests, including hemoglobin, leukocytes, and platelets, did not demonstrate a statistically significant difference between the case and control groups. Nevertheless, the case group exhibited higher leukocyte counts than the control group. The results of laboratory tests for procalcitonin, lactate, and albumin also did not reveal a statistically significant difference between the case and control groups. However, the mean levels of procalcitonin and lactate were slightly higher in the case group than in the control group. Notably, the evaluation of vitamin D and VDBP levels showed significant statistical differences between the case and control groups, with the levels of vitamin D and VDBP tending to be lower in the case group compared to the control group.

Table 2. Comparison of laboratory evaluation between groups.

Characteristics	Groups		p-value (independent t-test)
	Case (mean±SD)	Control (mean±SD)	
Haemoglobin (g/dL)	10.15±1.0	10.56±1.8	0.122
Leukocytes (10^3/mm^3)	14.22±1.3	13.94±1.5	0.112
Platelets (10^3/mm^3)	208.5±15.5	207.9±18.8	0.099
Procalcitonin (ng/mL)	15.73±2.9	13.44±3.2	0.089
Lactate (mmol/L)	2.7±0.8	2.3±1.5	0.101
Albumin (g/dL)	2.60 ± 0.64	2.73 ± 0.70	0.178
Vitamin D (ng/mL)	17.32 ± 1.72	23.65 ± 1.87	0.003*
VDBP (μg/mL)	162.39 ± 14.72	223.56 ± 17.71	0.002*

The data are shown as mean±SD. *P< 0.05. (VDBP: vitamin D binding protein; SD: standard deviation).

Table 3 illustrates the relationship between VDBP levels and mortality in sepsis patients. In the case group (comprising patients who did not survive), it was observed that the majority of the study subjects had VDBP levels less than 200 μg/mL. In contrast, within the control group (consisting of patients who survived), most patients had VDBP levels exceeding 200 μg/mL. A significant relationship between VDBP levels and mortality in sepsis patients was established, with P< 0.05. Patients with VDBP levels less than 200 μg/mL had a 2.17 times greater risk of mortality compared to patients with VDBP levels exceeding 200 μg/mL.

Table 3. The relationship between VDBP level and mortality in sepsis.

VDBP level	Groups		p-value (chi-square)	OR (95% CI)
	Case	Control		
< 200 μg/mL	29 (72.5%)	12 (30%)	0.002*	2,17 (1.92-11,54)
> 200 μg/mL	11 (27.5%)	28 (70%)		

*****Statistically significant, P< 0.05. (VDBP: vitamin D binding protein; OD: odd ratio; CI: confidence interval).

Table 4 displays the relationship between vitamin D levels and mortality in sepsis patients. Within the case group, the majority of study subjects had vitamin D levels less than 20 ng/mL. Conversely, in the control group, most patients had vitamin D levels exceeding 20 ng/mL. A significant relationship between vitamin D levels and mortality in sepsis patients

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was identified, with P< 0.05. Patients with vitamin D levels less than 20 ng/mL had a 2.54 times greater risk of mortality than subjects with vitamin D levels exceeding 20 ng/mL.

Table 4. The relationship between vitamin D level and mortality in sepsis.

Vitamin D level	Groups		p-value (chi-square)	OR (95% CI)
	Case	Control		
< 20 ng/mL	27 (67.5)	11 (27.5)	0.003*	2.54 (1.72-9.87)
> 20 ng/mL	13 (32.5)	29 (72.5)		

*****Statistically significant, P< 0.05. (OD: odd ratio; CI: confidence interval).

Discussion

Table 3 illustrates the relationship between VDBP levels and mortality in sepsis patients. In the case group (comprising patients who did not survive), it was observed that the majority of the study subjects had VDBP levels less than 200 μg/mL. In contrast, within the control group (consisting of patients who survived), most patients had VDBP levels exceeding 200 μg/mL. A significant relationship between VDBP levels and mortality in sepsis patients was established, with P< 0.05. Patients with VDBP levels less than 200 μg/mL had a 2.17 times greater risk of mortality compared to patients with VDBP levels exceeding 200 μg/mL.

Table 4 shows the relationship between vitamin D levels and mortality in sepsis patients. In the case group, it was found that most of the study subjects had vitamin D levels less than 20 ng/mL. Meanwhile, in the control group, it was found that most of the patients had vitamin D levels more than 20 ng/mL. There was a significant relationship between vitamin D levels and mortality in sepsis patients, P< 0.05. Patients with vitamin D levels less than 20 ng/mL had a 2.54 times greater mortality risk than subjects with vitamin D levels more than 20 ng/mL.

Table 4 displays the relationship between vitamin D levels and mortality in sepsis patients. Within the case group, the majority of study subjects had vitamin D levels less than 20 ng/mL. Conversely, in the control group, most patients had vitamin D levels exceeding 20 ng/mL. A significant relationship between vitamin D levels and mortality in sepsis patients was identified, with P< 0.05. Patients with vitamin D levels less than 20 ng/mL had a 2.54 times greater risk of mortality than subjects with vitamin D levels exceeding 20 ng/mL.

The current study was conducted to determine the role of VDBP expression and vitamin D levels in the mortality of septic patients. The results of this study indicate that VDBP and vitamin D levels have a significant role in predicting mortality in septic patients. VDBP and vitamin D levels tend to decrease in sepsis patients who experience mortality. The mortality risk in sepsis patients is approximately two times increased in patients with VDBP levels < 200 μg/mL and vitamin D levels < 20 ng/mL. Some studies support the relationship between VDBP and vitamin D levels in septic patients (19,20). Several studies have shown that VDBP and vitamin D level changes can affect sepsis severity, prognosis, and patient's immune response (5,21). A previous study found that low VDBP levels at the onset of sepsis were associated with an increased risk of death within 28 days and a higher severity of sepsis (14). In addition, this study also showed that there was a positive correlation between VDBP levels and vitamin D levels in septic patients. These results indicate that VDBP may play a role in vitamin D transport and influence the body's immune response to infection in septic patients. Another study also found that low VDBP levels at the onset of sepsis were associated with an increased risk of death within 28 days and increased severity of sepsis. In addition, this study also showed a negative

[DOI: 10.61186/rbmb.12.3.366]

relationship between VDBP levels and levels of inflammatory biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP) (22). These results suggest low VDBP levels may affect septic patients' inflammatory response and immune system.

However, several studies show conflicting results, with studies showing the effect of VDBP and vitamin D on the inflammatory response (23,24). These studies indicate that no significant relationship exists between VDBP and vitamin D levels in some cases of septic patients. Several studies indicate that although VDBP and vitamin D levels may change during sepsis, the relationship between the two with disease severity and clinical outcome in septic patients is unclear (24,25). Despite fluctuations in VDBP and vitamin D levels during sepsis, this study concludes that these changes may result from a systemic inflammatory response rather than a factor directly related to disease severity. These studies suggest that although VDBP and vitamin D play essential roles in the immune system, their relationship to sepsis may be complex and influenced by many other factors. The causes of this dysfunctional association may involve factors such as altered vitamin D metabolism, organ failure, and a strong inflammatory response in septic patients (20.22).

However, the current study has some limitations. It was conducted at one research center, so the results is limited to generalize. In addition, this study did not perform serial measurements of VDBP and vitamin D levels. This study also did not explore the history of vitamin D supplementation or consuming foods or drinks rich in vitamin D and did not explore sun exposure.

In conclusion, our findings demonstrated that low vitamin D binding protein and vitamin D increase mortality risk in septic patients. However no significant differences found in others clinicopathological features between the case and control groups. We believe that biochemical analysis of vitamin D binding protein and vitamin D level could be an useful screening assay for predicting patient prognosis, especially mortality in sepsis. Furthermore, more research in larger number of patients is requires to determine the prognostic value of vitamin D binding protein and vitamin D in septic patients.

The present study aimed to investigate the role of VDBP expression and vitamin D levels in the mortality of septic patients. The results of this study suggest that VDBP and vitamin D levels play a significant role in predicting mortality in septic patients. These levels tend to decrease in sepsis patients who do not survive. The risk of mortality in septic patients is approximately two times higher in those with VDBP levels < 200 ng/mL and vitamin D levels < 20 ng/mL. Some studies support the association between VDBP and vitamin D levels in septic patients (19,20). Several studies have demonstrated that alterations in VDBP and vitamin D levels can impact sepsis severity, prognosis, and the patient's immune response (5,21). A previous study found that low VDBP levels at the onset of sepsis were linked to an increased risk of death within 28 days and greater sepsis severity (14). Additionally, this study revealed a positive correlation between VDBP levels and vitamin D levels in septic patients, suggesting that VDBP may play a role in vitamin D transport and influence the body's immune response to infection in septic patients. Another study also reported that low VDBP levels at the onset of sepsis were associated with an increased risk of death within 28 days and greater sepsis severity. Furthermore, this study showed a negative relationship between VDBP levels and inflammatory biomarkers such as interleukin-6 (IL-6) and C-reactive protein (CRP) (22), suggesting that low VDBP levels may affect septic patients' inflammatory response and immune system.

Nevertheless, some studies have produced conflicting results, with findings indicating the effect of VDBP and vitamin D on the inflammatory response (23,24). These studies suggest that there may be no significant relationship between VDBP and vitamin D levels in certain cases of septic patients. Some studies indicate that although VDBP and

[DOI: 10.61186/rbmb.12.3.366]

vitamin D levels may change during sepsis, the relationship between these levels and disease severity and clinical outcomes in septic patients remains unclear (24,25). Despite fluctuations in VDBP and vitamin D levels during sepsis, it is concluded in this study that these changes may result from a systemic inflammatory response rather than being directly related to disease severity. These studies suggest that while VDBP and vitamin D play crucial roles in the immune system, their relationship with sepsis may be complex and influenced by many other factors. The causes of this complex association may involve factors such as altered vitamin D metabolism, organ failure, and a robust inflammatory response in septic patients (20.22).

However, this study has several limitations. It was conducted at a single research center, which limits the generalizability of the results. Additionally, this study did not include serial measurements of VDBP and vitamin D levels. The study also did not investigate the history of vitamin D supplementation, consumption of vitamin D-rich foods or drinks, and sun exposure.

In conclusion, our findings demonstrate that low vitamin D binding protein and vitamin D levels increase the risk of mortality in septic patients. However, no significant differences were found in other clinicopathological features between the case and control groups. We believe that the biochemical analysis of vitamin D binding protein and vitamin D levels could serve as a useful screening assay for predicting patient prognosis, particularly in terms of mortality in sepsis. Furthermore, further research involving a larger number of patients is required to establish the prognostic value of vitamin D binding protein and vitamin D in septic patients.

Acknowledgement

All authors thank the Department of Anaesthesiology and Intensive Care, Dr. M. Djamil General Hospital, Padang, Indonesia.

Funding

No financial support was received.

Conflict of interest

The authors declare that they have no conflict of interest.

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[DOI: 10.61186/rbmb.12.3.366]

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[DOI: 10.61186/rbmb.12.3.366]