

**The Effect of Vitamin D Supplementation on Autoimmune Bullous Skin Disorder Intensity Score on Bullous Pemphigoid and Acute Kidney Injury: A Case Report****Kartika Soka Rahmita<sup>1\*</sup>, Diyah Eka Andayani<sup>1</sup>, Diana Sunardi<sup>1</sup>**<sup>1</sup>Department of Nutrition, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia**ARTICLE INFO****Keywords:**

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**A B S T R A C T**

**Introduction:** Bullous pemphigoid is the most common bullous-type autoimmune disease. Hypovitaminosis D is often associated with autoimmune disease and found in 86,7% bullous pemphigoid patients. Vitamin D supplementation in bullous pemphigoid patients ought to ameliorate its clinical symptoms. **Case presentation:** A-58 years old male patient with bullous pemphigoid and acute kidney injury admitted with a chief complaint of infected blisters all over the body. The patient had been treated for 1 week with worsening swallowing pain and low intake. On the 12th day of hospitalization, the patient was given calcitriol supplementation of 0,25 mcg per day. There was an improvement in clinical symptoms shown on autoimmune bullous skin disorder intensity score (ABSIS) from 57 on inpatient day 7 to 17.5 on inpatient day 20. Patient discharged on the 20th day of hospitalization with no emerging blisters and the ability to swallow minced food by mouth. **Conclusion:** Calcitriol supplementation of 0,25 mcg per day for 10 days helps to improve the ABSIS score in bullous pemphigoid patient with acute kidney injury. Administration of calcitriol is considered safe and well tolerated.

**1. Introduction**

Bullous pemphigoid (BP) is one of the frequently occurring blistering skin diseases caused by autoimmune processes and characterized by tense blisters on erythematous skin, often accompanied by intense itching.<sup>1</sup> The global incidence of BP in 2022 is estimated to be 8.2 cases per 1,000,000 people, while in Asia, it is reported to be 5.6 cases per 1,000,000 people. However, there is currently no incidence data for BP in Indonesia.<sup>2</sup>

Malnutrition can occur in BP patients due to eating disorders caused by lesions in the digestive tract, increased catabolism, fluid, and electrolyte imbalance due to leakage from the lesions, and long-term corticosteroid therapy.<sup>3</sup> Although BP lesions more frequently occur in the lower extremities, they can affect mucous membranes in 10–35% of cases, especially in the buccal mucosa, leading to dietary

disturbances. Reduced nutritional status in BP patients can increase morbidity and mortality, especially since the prevalence of BP is higher in the elderly.<sup>4</sup>

One common condition in autoimmune patients is hypovitaminosis D. Decreased levels of vitamin D in the blood can result in dysregulation of the immune response. Vitamin D plays an immunomodulatory role in autoimmune diseases by controlling inflammation through the reduction of proinflammatory cytokine production from macrophages.<sup>5</sup> Vitamin D supplementation can inhibit Th1 cytokines and increase Th2 cytokines, resulting in modulating the immune response. Calcitriol, given as a form of vitamin D supplementation to patients with acute kidney injury, may improve vitamin D levels and its function in bullous pemphigoid patients.



## 2. Case Presentation

A 58-year-old male patient presented to the Emergency Department of RSCM on February 16<sup>th</sup>, 2023, with the main complaint of right-sided body weakness for the past 4 days. The patient reported slurred speech, difficulty articulating words during conversation, suppurating blisters, and increased difficulty breathing over the past 2 days. Upon examination in the Emergency Department, the patient was moderately ill and conscious with Glasgow coma scale (GCS) of E4M6Vaphasia. Vital signs included a blood pressure of 141/81 mmHg, pulse rate of 79 beats/minute, respiratory rate of 16 breaths/minute, temperature of 36.6 degrees Celsius, and oxygen saturation of 99% on room air. Dermatological examination revealed oral mucosa region: Hemorrhagic vesicles-bullae, multiple; ear, chest, abdomen, back, bilateral arms (flexor and extensor sides), back of hands, bilateral legs (flexor and extensor sides), back of feet: Tense bullae, multiple, clear-cloudy, with an erythematous base similar to discreet skin color, accompanied by erosion-excoriation-crusts ranging from red to black. Pain visual analog scale (VAS) for the erosion on the back is 1; Nikolsky sign: negative; Body surface area (BSA): 6%. In this patient, bullous lesions were found extending to the gastrointestinal tract, leading to a

decrease in food intake, especially over the past week during hospitalization. The lesions are most prevalent in the upper and lower extremities, presenting as blisters with erythematous bases, some of which have already eroded and are discharging pus. The patient complains of itching and a burning sensation in the areas where the lesions have ruptured, making mobilization difficult. The severity of the disease in the case patient was assessed using the autoimmune bullous skin disorder intensity score (ABSIS).<sup>6</sup>

The laboratory results of this patient were Hemoglobin 10.1 g/dL, leucocyte 16480/ $\mu$ L, thrombocyte 386000/ $\mu$ L, natrium 137 mEq/L, potassium 7.1 mEq/L, albumin 3.6 g/dL, blood glucose 267 mg/dL, ureum 117.7 mg/dL, creatinine 2.2 mg/dL, estimated glomerular filtration rate 31.8 mL/min/1.73m<sup>2</sup>.

The primary diagnosis by the attending physician was bullous pemphigoid, with differential diagnoses including epidermolysis bullosa acquisita, linear IgA bullous dermatosis with secondary infection, motor aphasia, and right-sided hemiparesis due to ischemic stroke (onset day-7), and acute kidney injury with differentials including acute-on-chronic kidney disease. Subsequently, the patient was admitted to the stroke unit.



Figure 1. Skin condition before vitamin D supplementation (inpatient day 7).



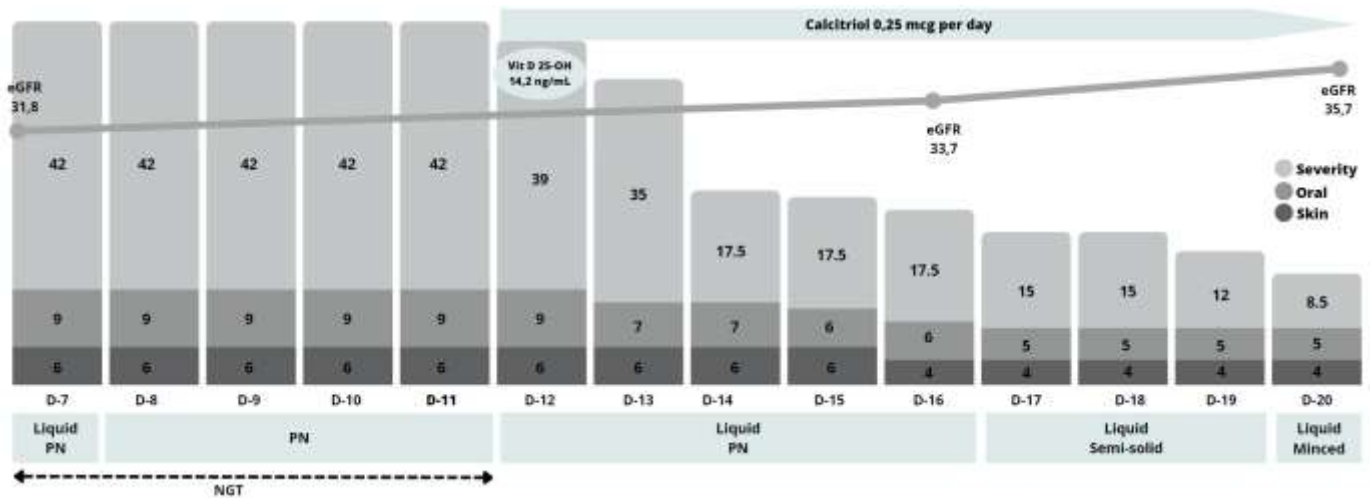


Figure 2. Inpatient monitoring based on nutrition intake, ABSIS, and kidney function.

On the inpatient day 1, the patient's ABSIS score was 31, attributed to erosive and pus-filled blister lesions covering 6% of the body surface area (BSA), along with lesions in the lips and oral cavity. However, the patient could still consume soft and liquid food without pain. By the inpatient day 5, the patient began having trouble swallowing due to pain, leading to a decline in food intake, and subsequently, a nasogastric tube (NGT) was inserted. The patient was treated for 1 week with worsening swallowing pain and low intake. On the inpatient day 7, the patient was consulted with the clinical nutrition department, and the ABSIS score was 57. This was attributed to blister lesions starting to dry and form crusts over 6% of the BSA, with lesions extending to the esophagus. The patient reported pain when consuming liquid food, even with the use of NGT. On the inpatient day 8, the patient experienced melena, prompting fasting as per the treating physician's advice, and the patient received total parenteral nutrition. On the inpatient day 12, the ABSIS score was 54, with easily bleeding pemphigoid lesions found up to the esophagus on esophagogastroduodenoscopy (EGD). The patient began receiving oral liquid food, and intake tolerance was deemed satisfactory. In this case patient, the

examination revealed a serum 25(OH)D level of 14.2 ng/mL, indicating vitamin D insufficiency. Risk factors for vitamin D insufficiency in the patient include the presence of autoimmune disease, insufficient sunlight exposure, kidney dysfunction, diabetes mellitus, long-term corticosteroid use, and physical inactivity. The patient start given calcitriol supplementation of 0,25 mcg per day. On the inpatient day 16, there was improvement in the patient's lesions, covering 4% of the BSA, and the patient reported relief from pain while consuming liquid food, resulting in an ABSIS score of 27.5. By the inpatient day 17, the patient no longer required supplemental parenteral nutrition and could consume liquid and soft food orally. On the inpatient day 20, the ABSIS score showed further improvement, reaching 17.5, and the patient could tolerate a diet consisting of steamed rice with minced meat well. There was an improvement in clinical symptoms shown on autoimmune bullous skin disorder intensity score (ABSIS) from 57 on the inpatient day 7 to 17.5 on the inpatient day 20. Patient discharged on the 20th day of hospitalization with no emerging blisters and the ability to swallow minced food by mouth.





Figure 3. Skin condition after vitamin D supplementation (inpatient day 20).

### 3. Discussion

In bullous pemphigoid, the production of autoantibodies bound to transmembrane protein (BP180) and hemidesmosome plaque (BP230) occurs, activating the complement system, recruiting inflammatory cells (especially eosinophils and neutrophils), and forming subepidermal blisters. The exact cause of PB autoantibody induction remains unclear, but it is suggested that T helper 1 (Th1) cytokines, particularly interferon- $\gamma$  (IFN- $\gamma$ ), can induce the secretion of immunoglobulins (IgG1 (IgG1) and IgG2. Meanwhile, T helper 2 (Th2) cytokines, including interleukin (IL)-4, IL-5, and IL-13, regulate the secretion of IgG4 and IgE. The binding of IgG autoantibodies to the basement membrane zone activates the classical complement pathway, leading to leukocyte chemotaxis and mast cell degranulation. Additionally, IgE plays a role in mast cell degranulation, causing eosinophil chemotaxis through mediators like eosinophil chemotactic factor of anaphylaxis.<sup>4</sup>

The severity of the disease in the case patient was assessed using the autoimmune bullous skin disorder intensity score (ABSIS) as it has proven to be more effective in depicting the patient's clinical condition by incorporating both subjective and objective assessments. ABSIS scoring ranges from 0 to 206, derived from three categories: the assessment of the extent of body surface area affected by lesions and

identification of lesion types, involvement of lesions in the oral cavity, and the patient's comfort in consuming various food or drink textures.<sup>6</sup>

Bullous pemphigoid (BP) generally has the potential to resolve spontaneously even without treatment, but it can persist for up to 3–6 years. However, untreated BP can increase mortality rates in elderly patients when active blisters are present. The therapeutic goals for BP patients are to heal existing lesions and prevent the formation of new ones.<sup>7</sup> Meanwhile, nutritional medical therapy for BP patients aims to prevent malnutrition or maintain the nutritional status of the patient. Malnutrition may occur in BP patients due to feeding difficulties caused by lesions in the gastrointestinal tract, increased catabolism resulting from epidermal detachment or the potential presence of neoplasms, fluid, and electrolyte imbalance due to fluid leakage through skin lesions, increased need for vitamin D and calcium, and various other nutritional factors that can influence disease progression depending on their underlying causes.<sup>3</sup>

The micronutrient requirements for bullous pemphigoid patients increase, particularly for vitamin D and calcium, due to the elevated risk of osteoporosis associated with the long-term use of high-dose corticosteroids. Hypovitaminosis D lowered innate and adaptive immunity which increases the risk of autoimmune diseases. According to Tukaj et al.,<sup>8</sup>



hypovitaminosis D is often associated with an increased prevalence of autoimmune diseases and was found to occur in 86.7% of BP patients. According to Yamamoto et al.,<sup>9</sup> there is a negative correlation between serum vitamin D levels and the severity of the disease. This study suggests that vitamin D3 can inhibit the expression of desmoglein-3 in the skin. Therefore, vitamin D3 supplementation is expected to serve as an adjuvant therapy for bullous pemphigoid patients, although further research is deemed necessary.<sup>9</sup>

Vitamin D plays a crucial role in immunomodulation in autoimmune diseases by controlling inflammatory conditions through the reduction of proinflammatory cytokine production by macrophages. Calcitriol, the active form of vitamin D, can modulate the activity of immune cells expressing the vitamin D receptor (VDR) and serves as an immunoregulator in the maturation and migration processes of various dendritic cell subtypes, as well as in VDR-mediated chemokine production. Activation of the vitamin D receptor inhibits the differentiation and maturation of dendritic cells, reduces the production of proinflammatory cytokines (IL-6, IL-12, and IL-23) and tumor necrosis factor-alpha (TNF- $\alpha$ ), and enhances the production of anti-inflammatory cytokines (IL-8 and IL-10). It also decreases the expression of major histocompatibility complexes class I and II, surface costimulatory molecules (CD40, CD80, CD83, and CD86), and inhibits the differentiation of plasma B cells, thereby reducing antibody formation. Vitamin D also influences T lymphocytes by suppressing Th1 and Th17 activities while promoting the differentiation of Th2 into CD4+ cells that produce IL-4. The active form of vitamin D, calcitriol, can regulate immune responses.<sup>10</sup> A decrease in serum 25-hydroxy-vitamin D (25(OH)D) levels can lead to immune response dysregulation and an increased risk of autoimmune diseases.<sup>5</sup>

From the research by Bleizgys et al.<sup>11</sup> emphasizes that vitamin D from sunlight and dietary intake cannot fully replace serum vitamin D deficiencies. Therefore, vitamin D supplementation in adult patients with

insufficiency or deficiency is recommended at 6000 IU/day for 3 months or 50,000 IU/week for 2 months, with a tolerable upper daily dose of 10,000 IU. The examination of 25(OH)D levels should be repeated after 1–1.5 months following supplementation to assess the effectiveness of the supplementation and prevent the occurrence of vitamin D toxicity. Supplementation with vitamin D3 in BP patients is said to reduce the expression of the BP320 gene through post-transcriptional mechanisms. Similarly, supplementation with calcitriol can decrease the release of proinflammatory cytokines such as IL-6 and IL-8 produced by PB IgG.<sup>5</sup> This aligns with findings from the study by Yamamoto et al.,<sup>9</sup> which stated that vitamin D3 supplementation in BP patients with hypovitaminosis D can have a downregulating effect on the expression of the BPAG1 gene. BPAG1 is a component of hemidesmosomes that influences the integrity of the basement membrane zone and improves the condition of skin lesions. Vitamin D supplementation in AKI patients is also suggested to have renoprotective effects. According to Xu et al.,<sup>12</sup> vitamin D supplementation can improve AKI conditions as an antioxidant by increasing glutathione (GSH), superoxide dismutase (SOD)-1 and SOD-2, reducing nitric oxide synthase (iNOS), and engaging in antiapoptotic mechanisms. Due to kidney dysfunction in the patient, vitamin D supplementation is provided in the form of calcitriol, the metabolically active form of vitamin D. Although there is currently no official recommended dosage for vitamin D supplementation in patients with kidney impairment, Pavlovic et al.,<sup>13</sup> recommend the initiation of calcitriol at a low initial dose of 0.25–0.5 mcg per day orally, with regular monitoring of parathyroid hormone (PTH) and calcium levels.

The patient was discharged on the inpatient day 20 with improved skin lesions covering 4% of the body surface area (BSA), recovery of gastrointestinal lesions, decreased pain, and increased ability of the patient to consume food with a denser consistency. As a result, the ABSIS score for the case patient showed improvement, reaching 17.5.





#### 4. Conclusion

In cases of autoimmune diseases, including bullous pemphigoid, hypovitaminosis D is frequently observed, suspected to play a role as one of the contributing factors to disease relapse due to immune response dysregulation. Vitamin D supplementation can inhibit Th1 cytokines and increase Th2 cytokines result in modulating the immune response. Calcitriol given as a form of vitamin D supplementation to patients with acute kidney injury may improve vitamin D levels and its function in bullous pemphigoid patient. After 10 days of calcitriol supplementation, the ABSIS improved with preserved kidney function. Corticosteroid treatment was delayed because of the high level of inflammation. Calcitriol supplementation of 0.25 mcg per day for 10 days helps to improve the ABSIS score in bullous pemphigoid patients with acute kidney injury in this case report. Administration of calcitriol is considered safe and well tolerated.

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