World Nutrition Journal | eISSN 2580-7013

ORIGINAL PAPER

Medical nutrition therapy in hospitalized patients with pemphigus vulgaris

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Received 17 March 2023
Accepted 16 May 2023
Published 31 August 2023

Link to DOI:
10.25220/WNJ.V07.i1.0004

Citation: Anindhita B, Manikam N R M. Medical nutrition therapy in hospitalized patients with pemphigus vulgaris. World Nutrition Journal.2023 August 31, 7(i1): 14-22.

Website : http://www.worldnutrijournal.org/

Abstract

Dysphagia due to involvement of the oral, pharyngolaryngeal, and esophageal mucosa and increased catabolism due to epidermal shedding can contribute to a decline in nutritional status in pemphigus vulgaris (PV) patients. On the other hand, decreased lean body mass is associated with immune system impairment, increased risk of infection, and delayed wound healing in PV patients, therefore, nutritional screening and assessment are necessary. Medical nutritional therapy in PV patients aims to overcome the metabolic response to the insults, prevent further malnutrition, modulate the immune system, and accelerate wound healing process. An aggressive nutritional support to minimize protein loss during the phase of mucocutaneous lesion healing is needed in patients with PV. Aside from macronutrient adequacy, micronutrients including vitamin A supplementation can be considered to accelerate wound healing process. Medical nutritional therapy including provision of adequate macronutrients, micronutrients, addressing dehydration and electrolyte imbalances should be the cornerstone of multidisciplinary treatment in PV patients.

Keywords: malnutrition, medical nutrition therapy, pemphigus vulgaris, micronutrients, wound healing

Background

Pemphigus vulgaris (PV) is one of the most commonly found autoimmune bullous disease, with an incidence of up to 70% of all pemphigus cases.[1,2] Study by Budianti et al.[3] in referral hospital in Indonesia also showed similar results, with pemphigus vulgaris being the most commonly found type of pemphigus (75%). The use of corticosteroids as the main therapy for PV has led to a drastic decrease in PV mortality, from 75% to 30%. However, currently there is a shift in the causes of pemphigus mortality from the direct effects and severity of the disease to long-term complications.[1,2] This is due to the long-term use of steroids, which can cause various complications such as hyperglycemia, osteoporosis, hypertension, edema, adrenal suppression, and delayed wound healing. [4–7]

Involvement of the oral, pharyngolaryngeal, and esophageal mucosa in PV patients can induce dysphagia and contribute to a decline in nutritional status in patients with PV. Increased catabolism due to epidermal shedding, protein loss, inflammatory responses, and physical immobilization can also increase the risk of malnutrition and sarcopenia in pemphigus patients.[8,9] Furthermore, malnutrition can also affect wound healing in pemphigus patients. Decreased lean body mass is associated with immune system impairment, increased risk of infection, and delayed wound healing.[10]

Medical nutritional therapy in PV patients aims to overcome the metabolic response to the insults, prevent further malnutrition, modulate the immune system, and accelerate wound healing process. In addition to adequate macronutrient intake, micronutrient supplementation including vitamin A is associated with the wound healing process. Vitamin A is also associated with modulating the immune system through the effects of proliferation, differentiation, and apoptosis of immune cells, thus playing a role in modulating pemphigus.[11] However, to this day literature on vitamin A supplementation specifically for patients with pemphigus vulgaris is still limited. Therefore, this review article will discuss medical nutritional therapy in patients with pemphigus vulgaris, specifically the role of vitamin A in wound healing in order to achieve optimal clinical outcomes.

Pemphigus Vulgaris

Pemphigus vulgaris is a chronic autoimmune disease that belongs to the group of autoimmune bullous diseases (AIBD). It is initiated by an autoantibody response with the accumulation of immunoglobulin G (IgG) on the skin. Exposure of autoantibodies to autoantigens triggers the formation of immune complexes, which subsequently cause damage to the skin integrity, leading to the formation of blisters and further infiltration of immune cells. Both the innate and adaptive immune systems are involved in the autoimmune response and inflammation in the pathogenesis of AIBD. In patients with PV, there are abnormalities in the ratio and function of T cell subsets in circulation. There is an increase in the levels of Th17 cells that secrete IL-17, which promotes an inflammatory response, and a decrease in Treg cells that inhibit Dsg3-autoreactive T cell proliferation and antibody production which prevent autoimmune disease.[12]

Several external factors can initiate and prolong the course of pemphigus vulgaris, including drugs, viral infections (herpes simplex), physical agents, contact allergens, vaccination, dietary factors, and psychological stressors.[13] Genetic contributions are also associated with the pathogenesis of pemphigus vulgaris, as it can be found in other autoimmune diseases, including autoimmune thyroid disease, type 1 diabetes, and rheumatoid arthritis. Several dietary factors can also induced PV in patients with genetic susceptibility such as allium vegetables, phenols, tannins and cinnamic acid.[14]

The clinical manifestations of pemphigus vulgaris generally start from the oral mucosa and can take several months prior to the appearance of skin lesions. The lesions can then be localized for several months until generalized listers appear.[15] Acute eruptions in the form of generalized bullae that appear from the beginning are rare. Skin bullae are usually flaccid and non-pruritic with erythematous or non-erythematous bases that can quickly develop into bloody erosions. These lesions can be focal or generalized and there is a sensation of burning and pain on the erosions or ruptured bullae. The flexural regions and extremities, which are vulnerable to stress and trauma, are common sites for pemphigus vulgaris.[2,9] Lesions on the oral mucosa often cause pain and can lead to decreased food intake in PV patients.[15]

One of the characteristics of PV lesions is the erosion can spread to previously healthy skin. This phenomenon is called Nikolsky sign and occurs when the bullae rupture and the bulla wall is pulled towards the periphery of the active lesion. [15,16] Unlike lesions caused by viral infections or stomatitis that can heal within a few days, lesions in pemphigus usually cannot heal on their own.[7] The spread of lesions can lead to complications such as infections, which can prolong the healing process.[7,16–18]

The diagnosis of PV can be established through a clinical examination and various diagnostic modalities such as skin and mucous membrane biopsy, immunopathology examination, and serum autoantibody examination. Biopsy examination can reveal suprabasal keratinocyte separation, triggering basal cell layer separation and vesicles that contain separated and round-shaped keratinocytes (acantholytic). Immunopathology examination using immunofluorescence can show the presence of immunoglobulin G and sometimes C3 deposits on skin lesions. Autoantibody examination also usually shows an increase in detected IgG.[15]

The management of PV involves administering glucocorticoids until no new bullae form and Nikolsky sign disappears. The initial systemic corticosteroid therapy with 0,5–1 mg/kgBW/day of prednisone and 1 to 1,5 mg/kgBW/day is recommended in patients with mild PV and patients with more moderate to severe PV, respectively.[15,19] The glucocorticoid dosage should then be gradually tapered down to reach the minimum effective maintenance dose. Patients may also be given other immunosuppressants as steroids sparing-agents. Management also includes wound care, administration of antibiotics to patients with secondary infections, as well as fluid and electrolyte management. Monitoring of PV patients includes improvement in skin lesions and side effects of treatment. Laboratory monitoring also includes pemphigus antibody titers, as well as hematologic and metabolic indicators of glucocorticoid side effects.[15]

Nutritional Problems

The clinical manifestations of pemphigus can involve the oral mucosa, epidermis, or both.[20] The involvement of mucous membranes, especially the oral mucosa and upper gastrointestinal tract such as the esophagus, can affect the patient's ability to eat, including chewing and swallowing, leading to malnutrition and electrolyte imbalances, thereby increasing the severity of the disease. In addition, increased catabolism due to epidermal shedding can also increase the risk of malnutrition and sarcopenia in patients with pemphigus.[8,9] However, studies assessing the incidence of malnutrition and sarcopenia in patients with PV have not yet been found. The increased loss of protein due to extensive mucosal and cutaneous erosion, serous discharge from wounds, and increased catabolism can also lead to hypoalbuminemia in PV patients. Studies[21,22] showed that low albumin levels in pemphigus patients are associated with poor clinical outcomes.

Micronutrients including trace elements levels can also be affected in patients with PV. These could be secondary to poor nutritional intake or chronic inflammation.[14] Inflammation caused by acute or chronic diseases can trigger the redistribution of various micronutrients in circulation to organs, leading to a decrease in plasma micronutrient levels. The effect of inflammation on micronutrients can be short but can also persist in chronic diseases.[23] Severe skin lesions could also result in excessive loss of fluids which leads to dehydration, an imbalance of electrolytes and the loss of water-soluble micronutrients.[8,24]

Furthermore, a study by Moravvej et al. [25] also showed that suboptimal vitamin D status (<30 ng/mL) is commonly found in patients with pemphigus, and the risk of low vitamin D status is higher in patients with pemphigus with a large surface area of lesions and high Pemphigus Area and Activity Scores.

Side Effects of Glucocorticoid

Long-term use of systemic steroids in patients with autoimmune diseases can also increase the risk of hyperglycemia and drug-induced diabetes. High-dose administration of glucocorticoid, whether oral, inhaled, or topical, are associated with hyperglycemia and steroid-induced diabetes. Corticosteroids increase blood glucose levels by increasing hepatic gluconeogenesis and decreasing glucose uptake in peripheral tissues. In addition, acute exposure to corticosteroids can trigger insulin resistance by reducing the ability of adipocytes and hepatocytes to bind to insulin.The risk of hyperglycemia also increases with increasing daily steroid dose and cumulative dose.Glucose uptake and metabolism in peripheral tissues can return to normal when corticosteroid use is discontinued.[4,5]

Due to the increased activity of lipoprotein lipase that hydrolyzes circulating triglycerides such as chylomicrons and very low-density lipoproteins, long term used of glucocorticoids also result in an elevated amount of fatty acids in circulation. These fatty acids can then be distributed to ectopic fat locations and responsible for the occurrence of central adiposity.[6]

The use of immunosuppressants can inhibit several inflammatory mediators involved in the wound healing process, including IL-2, IL-4, IFN-gamma, and TNF alpha, thereby inhibiting T-cell activation. Corticosteroids can also affect

lymphocyte recirculation and trigger lymphocyte death, thereby contribute to delayed wound healing.[7]

Glucocorticoids can also lead to a decrease in bone formation and an increase in bone resorption through several mechanisms. First, glucocorticoids can reduce the differentiation and maturation of osteoblasts, leading to a decrease in the number and function of osteoblasts. In addition, glucocorticoids can induce apoptosis of osteoblasts, further contributing to a decrease in bone formation. Glucocorticoids can also induce apoptosis of osteocytes, which play a role in repairing microdamage to bones, further reducing bone quality. Up to 40% of patients receiving glucocorticoids may experience a decrease in bone mass. The secondary decrease in bone mass due to glucocorticoids can occur even from the beginning of use, and is most significant in the first six months. The initial rate of bone mass reduction can reach 12% in the first year of glucocorticoid use, with an average of 2-3% per year. The daily dose of glucocorticoids can predict the occurrence of fractures, with a dose as low as 2.5 mg of prednisone per day already increasing the risk of fractures, and a dose of more than 7.5 mg per day can increase the risk of fractures up to fivefold.[26]

Nutritional Assessment

Patients with pemphigus vulgaris (PV), especially those with involvement of the oral mucosa and gastrointestinal tract, are at an increased risk of malnutrition. Therefore, nutritional screening and assessment are necessary. Several methods are commonly used to screen for malnutrition in hospitalized patients, including MST, Nutritional Risk Screening (NRS), and Patient Generated Subjective Global Assessment (PG-SGA).[27]

Relying solely on Body Mass Index (BMI) as a way to evaluate nutritional status is considered insufficient for anticipating a decline in muscle mass and physical capabilities. Up to this point, there have been no studies that assess the sensitivity, specificity, and validity of nutritional diagnostic modalities in patients with PV. However, diagnostic modalities such as GLIM can be used as it assesses malnutrition based on etiological and phenotypic factors, which includes nonvolitional weight loss, low BMI, reduced muscle mass, reduced food intake or assimilation and disease burden or inflammation.[28]

It is also important to identify sarcopenia in chronic PV patients. The diagnosis of sarcopenia can be confirmed if a patient has low quantity and quality of muscle, based on body composition assessment using modalities such as magnetic resonance imaging (MRI), computed tomography (CT) scan, or by using dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA). [29]

Electrolytes laboratory examination is also necessary for PV patients due to the risk of electrolytes disturbances. It is also important to regularly monitor blood sugar and lipid profile as they can serve as metabolic indicators for the adverse effects of glucocorticoids. Considering the need for high protein therapy, kidney function tests should be considered as part of clinical examination to exclude any kidney disorders. Biochemical panel examination, including vitamin D, parathyroid hormone, and serum phosphate, can also be used as an initial step in predicting the occurrence of glucocorticoid-induced osteoporosis.[26]

Medical Nutrition Therapy

The main goal of managing autoimmune diseases such as pemphigus vulgaris is to induce remission, minimize treatment side effects, and improve patients' quality of life.[6] Medical nutritional therapy, as part of a multidisciplinary approach for pemphigus patients, aims to prevent further protein loss, improve nutritional status, optimize fluid and electrolyte balance, accelerate wound healing, and help prevent relapse.[8,30]

When the affected body surface area (BSA) is more than 30% or when at least two mucous membranes are affected, the condition can be categorized as severe. In addition, the response to injury increases metabolic needs and can raise energy requirements up to 250%.[10] In such cases, it is necessary to provide aggressive nutritional support to reduce protein loss and to aid in the healing of mucocutaneous lesions.[8,9]

Indirect calorimetry is the gold standard for determining resting energy expenditure (REE) in hospitalized patients. In situations where the use of indirect calorimetry is not possible, REE calculation can be done using weight-based equations of 30 kcal/kg body weight in malnourished patients. Energy administration needs to be increased gradually, especially in PV patients who have experienced decreased intake for some time due to dysphagia or odynophagia, which puts them at risk of developing refeeding syndrome.[31]

In addition to increased energy requirements, patients with extensive wounds also experience an increased protein requirements, up to 50%, due to significant protein loss. Moreover, protein is also required in the formation and activity of immune cells involved in the wound healing process. A decreased in lean body mass by 10% is associated with impaired immune function and an increased risk of infection. In cases where lean body mass decreases by more than 10%, there is a competition between wound healing process and the body's need to restore lean body mass. Patients who lose more than 30% of their lean body mass will experience delayed wound healing.[10]

Inadequate protein intake can slow down the progression of wound healing, especially from the inflammatory phase to the proliferative phase. In the proliferative and remodeling phases, energy and protein deficiency can also decrease fibroblast activity, slow down angiogenesis, and reduce collagen formation.[10] Therefore, patients with pemphigus vulgaris require more aggressive nutritional support to minimize protein loss during the phase of mucocutaneous lesion healing. Protein intake of up to 2-3 g/kg body weight per day can be considered for pemphigus patients.[8,30]

Adequate carbohydrate and fat intake is also needed to support the inflammatory response, cellular activity, angiogenesis, and collagen deposition in the proliferative phase of wound healing. Specifically, adequate carbohydrate intake is needed for fibroblast production and movement as well as leukocyte activity. Carbohydrates can also stimulate the secretion of hormones and growth factors, including insulin, which plays a role in the anabolic process in the proliferative phase.[10] Nevertheless, the choice of carbohydrates must still be taken into account because of the possibility of hyperglycemia and diabetes induced steroids in patients receiving steroids. Providing carbohydrates in the amount of 45-60% from high-fiber complex carbohydrates and avoiding simple carbohydrates may be considered in patients receiving long-term steroid therapy. [32]

Fat also plays a structural role in the cell membrane layer during tissue growth in wound healing process.[10] Just like carbohydrates, the selection of fat also needs to be considered in PV patients receiving steroids due to the risk of dyslipidemia and altered lipid metabolism.[6]

Replacing saturated fat with unsaturated fats such as monounsaturated fatty acids (MUFA) can be considered in patients on long-term steroid therapy to help manage hyperglycemia and dyslipidemia.[32] Polyunsaturated fatty acids (PUFAs) such as omega-3 have been shown to have anti-inflammatory effects. Metabolites of omega-3 PUFAs, such as resolvins (Rvs)-1 and Rvs2, have anti-inflammatory effects by inhibiting immune reactions and increasing the levels of Treg cells.[33] However, studies regarding omega-3 fatty acid supplementation doses specifically in patients with pemphigus vulgaris have not yet been found.

Avoiding hot foods and sharp foods such as chips and consuming soft foods can be done in patients with involvement of oral mucosa. Pemphigus vulgaris patients with malnutrition or those at risk of malnutrition who are unable to meet their energy needs through oral intake may benefit from the administration of oral nutrition supplements (ONS) to improve their clinical outcomes. ONS administration can help maintain muscle mass during treatment and significantly reduce post-treatment mortality in malnourished patients.[31] In cases where oral and gastrointestinal mucosal lesions caused a decrease in intake due to dysphagia or odynophagia, the placement of enteral nutrition access such as nasogastric tube (NGT) can be considered.[8,30] Restrictions of several dietary factors should be done cautiously as it could cause malnutrition or worsen the malnutrition.

Resuscitation with intravenous fluids to correct any dehydration should be addressed in the PV patients. Any electrolyte imbalance also needs to

be corrected in the PV patients.[24] Supplementation of micronutrients should be considered in PV patients, especially in those with reduced intake and cannot meet their micronutrient requirements from dietary intake. Vitamin B, including thiamine, riboflavin, pyridoxine, folic acid, pantothenic acid, and cobalamin, are essential factors in enzyme reactions involved in leukocyte formation and anabolic processes of wound healing. Thiamine, riboflavin, pyridoxine, and cobalamin are also needed in collagen synthesis. Therefore, inadequate intake of vitamin B indirectly affects the wound healing process by disrupting antibody production and white blood cell function, thereby increasing the risk of infection complications.[7] Therefore, supplementation with B complex vitamins can also aid in the wound healing process.

Vitamin C is an important cofactor in collagen biosynthesis and can protect endothelium by increasing collagen synthesis, maintaining endothelial vasodilation and barrier function. Vitamin C also plays a role in limiting the inflammatory response and aid in wound healing process.[23] Vitamin C deficiency can disrupt the immune response during the inflammatory phase of wound healing, increase capillary fragility, decrease collagen synthesis and elasticity needed in the proliferative and remodeling phases. Supplementation with 500 mg to 2 grams of vitamin C per day may be considered to aid wound healing. The beneficial effects of vitamin C supplementation can also be enhanced by co-supplementation with zinc. Zinc plays a role in the wound healing process through its role in DNA replication in cells with high proliferation rates, including epithelium and fibroblasts. Zinc is involved in fibroblast proliferation and epithelialization through the stimulation of enzymes. The recommended dose of zinc to accelerate wound healing can reach up to 40 mg per day. [34]

According to the American College of Rheumatology, adult patients who take prednisone at a dose of 2.5 mg or more per day for three months or longer should optimize their vitamin D intake with supplementation of 600-800 IU and calcium intake of 1000-1200 mg per day to prevent glucocorticoid-induced osteoporosis. The Endocrine Society guideline recommends vitamin D supplementation of 1500-2000 IU per day to consistently increase vitamin D levels above 30 ng/mL in patients at risk of vitamin D deficiency. However, studies showed that patients with autoimmune disease require higher dose of supplementation.[35,36]

The expression of the transcription factor FoxP3, which plays a crucial role in the differentiation and effector function of Treg cells, can be enhanced by vitamin D. In addition, T cells activated by vitamin D also exhibit decreased expression of IFNγ, IL-17 and IL-21, indicating suppression of inflammation.[37] Patients with autoimmune disease should have their 25(OH)D levels measured. A high initial dose of vitamin D (50,000 IU capsule once a week for 8 weeks) should be considered if the levels are less than 30 ng/mL followed by a maintenance phase with an initial dose of 800 IU/day is recommended.[38]

Currently, studies on the role of vitamin A in patients with PV have yet been found. However, vitamin A functions as a hormone that can influence the activity of epithelial cells, melanocytes, fibroblasts, and endothelial cells through its action on retinoic acid receptors (RARs). The need for vitamin A can increase sharply in cases of injury or acute stress.[39] Vitamin A is also associated with the modulation of the immune system through the effects of proliferation, differentiation, and apoptosis of immune cells, thus playing a role in modulating pemphigus by reducing Th17 cells and stabilizing regulatory T cells (Tregs).[11] Vitamin A, in the form of retinoic acid, can increase the expression of Foxp3 and act as a key regulator of TGF-β-dependent immune responses. It can also inhibit the production of IL-6, supporting the differentiation of anti-inflammatory Treg cells and inhibiting the expression of IL-17.[40,41]

Vitamin A also has beneficial effects associated with the wound healing process and its deficiency can disrupt the wound healing process. The beneficial mechanism of vitamin A in the wound healing process occurs through several pathways. Vitamin A can stimulate the growth of epithelial cells, fibroblasts, and granulation tissue. Vitamin A also plays a role in the differentiation of

keratinocytes into mature epidermal cells through its interaction with nuclear chromatin and gene expression.[40,42] Vitamin A facilitates the differentiation process of epithelial cells by increasing the number of monocytes and macrophages in the early inflammatory phase of the wound healing process.[34,39] Retinoic acid can also increase the production of extracellular matrix components such as type I collagen and fibronectin.[43]

Furthermore, high doses of corticosteroids can deplete vitamin A storage in the liver. As discussed earlier, corticosteroids can also delay wound healing process. Vitamin A can counteract the anti-inflammatory effects of corticosteroids on wound healing, therefore systemic or topical vitamin A supplementation may be considered in patients with acute or chronic wounds receiving immunosuppressive therapy to accelerate wound healing.[34,39,43]

The Dietary Recommendation Intake (DRI) for vitamin A is 700 mg or 2310 IU per day for women and 900 mg or 3333 IU per day for men. Specific guidelines and recommendations for administering vitamin A to PV patients have not been found. Nevertheless, administering vitamin A at a range of 10,000 to 50,000 IU per day orally or 10,000 IU intramuscularly for 10 days may be considered to accelerate wound healing.[34] Other literature recommends administering 15,000–20,000 IU of vitamin A per day for 14–21 days in patients with chronic steroid use. However, administration of high-dose vitamin A supplementation should only be given to patients with good liver and kidney function to prevent toxicity.[39]

In addition, regular nutritional monitoring is necessary for patients with PV and should include several aspects such as food intake, enteral feeding tolerance, anthropometric measurement, nutritional status, electrolyte and albumin levels, blood glucose levels, the presence of nutritional deficiency symptoms. Regular nutritional monitoring can help identify nutritional problems in PV patients, enabling timely intervention to prevent further complications.

Conclusion

The involvement of oroesophageal mucosa, increased catabolism, and severe skin lesions can all lead to malnutrition, dehydration, electrolyte imbalances and alteration of micronutrients. The used of glucocorticoids as principal therapy can also caused adverse effects including altered macronutrient metabolisms and delayed wound healing. An adequate medical nutrition therapy including macronutrients, micronutrients, addresing dehydration and electrolyte imbalances are needed as part of multidisciplinary treatment of pemphigus patients. Particularly, aside from macronutrient adequacy, micronutrients including vitamin A supplementation can be considered to accelerate wound healing process. Further clinical research is needed to regarding the role of vitamin A supplementation in wound healing, particularly in PV patients.

Conflict of interest

The authors declare that there is no conflict of interest related to the study.

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