Review

The Role of Nutrition in the Pathogenesis and Treatment of Autoimmune Bullous Diseases – A Narrative Review

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Posted Date: 29 July 2024

doi: 10.20944/preprints202407.2187.v1

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Review

The Role of Nutrition in the Pathogenesis and Treatment of Autoimmune Bullous Diseases—A Narrative Review

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Abstract: Autoimmune bullous diseases (AIBDs) are a group of conditions marked by the formation of blisters and erosions on the skin and mucous membranes. Knowing that, most of the AIBDs are severe and resistant to treatment, we decided to look upon the nutritional aspect as a light for the future for both - patients and clinicians. In this review, we would like to summarize the evidence of the role of nutrition in pathogenesis and treatment of the following AIBDs: i) pemphigus, ii) bullous pemphigoid and mucous membrane pemphigoid, iii) dermatitis herpetiformis, and iv) epidermolysis bullosa aqusita.

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1. Introduction

Autoimmune bullous diseases (AIBDs) are a group of conditions marked by the formation of blisters and erosions on the skin and mucous membranes. These diseases arise when the body's immune system erroneously targets proteins crucial for maintaining skin integrity, leading to the separation of skin layers and blister formation [1].

To date, AIBDs have been classified into various types and subtypes based on clinical, histopathological and immunological characteristics. Most of the AIBDs are severe and resistant to treatment. Therefore, often requiring a range of therapies including steroids, immunosuppressive medications or biological agents [2].

In this review, we would like to summarize the evidence of the role of nutrition in pathogenesis and treatment of the following ABIDs: i) pemphigus, ii) bullous pemphigoid and mucous membrane pemphigoid, iii) dermatitis herpetiformis, and iv) epidermolysis bullosa aqusita.

2. Characteristics of Selected Autoimmune Bullous Diseases

2.1. Pemphigus

2.1.1. Epidemiology and Etiopathogenesis

In Europe, the incidence of pemphigus is 0.5-8/1,000,000/year, it occurs in all age groups with the peak incidence around the age of 50-60, it affects women slightly more often. The most common variety is pemphigus vulgaris (70-80% of cases in Europe, the USA and Japan) [3]. Pemphigus is an autoimmune disease, potentially life-threatening, in which the immune system is dysregulated, and autoantibodies are formed against desmogleins, i.e. surface proteins of keratinocytes, namely

 doi:10.20944/preprints202407.2187.v1

desmoglein 3 and/or 1. The binding of these autoantibodies to desmogleins causes acantholysis (cleavage of intercellular junctions of the epidermis). The association with HLA antigens has been described. Exogenous factors that may cause pemphigus include drugs - mostly containing a thiol group (-SH), but also non-thiol drugs, e.g. penicillamine, angiotensin-converting enzyme inhibitors, calcium channel blockers, penicillin's, cephalosporins, non-steroidal anti-inflammatory drugs. Another triggering factors were described, for examples: burns, UV radiation; viral infections; vegetables from the Allium group containing sulfhydryl groups - garlic, leek, onion [4].

2.1.2. Clinical Picture

Pemphigus occurs in two main classic varieties - pemphigus vulgaris and foliaceus. The third variety is paraneoplastic pemphigus, which coexists with cancer, mainly non-Hodgkin's lymphoma and chronic lymphocytic leukemia. Pemphigus vulgaris is a potentially life-threatening disease due to the development of epidermal barrier disorders resulting in severe water and electrolyte disturbances and extensive secondary microbial infections. The introduction of glucocorticosteroids (GCS) into treatment in the second half of the 20th century significantly reduced the mortality rate due to this disease from 75% to 30%.

Pemphigus vulgaris initially manifests itself in 70-90% of cases with mucosal changes in the form of erosions resulting from easily bursting delicate blisters. Erosions are most often located on the mucous membranes of the oral cavity, less often also on the throat and the initial sections of the respiratory system, conjunctiva or the epithelium of the urogenital system. Patients often complain of swallowing problems and hoarseness. Usually, a few weeks after the appearance of mucosal lesions, blistering lesions appear on skin and/or scalp in the form of flaccid blisters that rupture easily into erosions. These, in turn, become covered with scabs and heal, leaving discoloration and without scarring [5].

The clinical picture of pemphigus foliaceus is dominated by superficial erosions covered with crusts and exfoliation. Due to their very superficial location in the epidermis, blisters are usually not present on the skin, only cracked covers cover the erosions with scabs. The lesions are located mainly in the upper chest and back, especially in the seborrheic areas, on the face and scalp. The lesions do not affect the mucous membranes.

Paraneoplastic pemphigus, as it coexists with cancer and has a significant predilection for affecting all mucous membranes, requires a special description. Erosions in the upper gastrointestinal tract often lead to the development of ulcerative stomatitis and swallowing disorders, which require a specialized dietary approach, which will be discussed in detail below. Less common types of pemphigus that do not require the implementation of different procedures in the patient's diet therapy will not be described in this chapter to maintain clinical clarity of autoimmune bullous diseases [6].

2.1.3. Diagnosis and Pharmacological Treatment

The diagnosis of pemphigus is based on the clinical picture of the lesions, the histopathological picture of skin and/or mucous membrane sections and the results of immunological tests, but the basic diagnostic test is the examination of a skin section using the direct immunofluorescence method, in which deposits of antibodies are observed, usually of the IgG class with the complement component C3 or without it, which are located in the intercellular spaces of the epidermis and epithelium. Serum testing using the indirect immunofluorescence method is used to determine the titer of pemphigus antibodies in the patient's serum. The concentration of anti-desmoglein 1 antibodies shows a closer correlation with the patient's clinical condition than anti-desmoglein 3 antibodies.

Rituximab an antibody directed against the CD-20 molecule, is currently the first-line drug in the treatment of paraneoplastic pemphigus. It is used as monotherapy or in combination with systemic glucocorticoids, which are classic drugs used in the treatment of pemphigus. GCS combined with immunosuppressive drugs, such as azathioprine or cyclophosphamide, is the basic therapy for

 doi:10.20944/preprints202407.2187.v1

other forms of pemphigus. Local treatment in the form of disinfectant and anti-inflammatory preparations is always used in the case of active lesions [7,8].

2.2. Bullous Pemphigoid and Mucous Membrane Pemphigoid

2.2.1. Epidemiology and Etiopathogenesis

Bullous pemphigoid (BP) is the most common autoimmune bullous disease, typically occurring in elderly people over 70 years of age, with no gender predilection. The incidence is estimated at 0.2-4 cases/100,000/year. Patients with pemphigoid often suffered from neurological and psychiatric diseases and cancer. Literature data indicate the possible occurrence of cross-immune reactions between skin and central nervous system antigens. The antigens in this autoimmune disease are hemidesmosomal proteins within the dermal-epidermal junctions with a molecular weight of 180 kD (BP180 antigen) and 230 kD (230BP antigen). When autoantibodies combine with antigens, the inflammatory cascade involving neutrophils, eosinophils and complement components is activated, which leads to damage to the dermal-epidermal junctions. Exogenous factors that may cause pemphigoid include: UV radiation, mechanical and thermal injuries; stress; viral infections; drugs - gliptins, PD1 inhibitors, fursemide, amoxicillin, ciprofloxacin, potassium iodide, gold salts, spironolactone. Mucous membrane pemphigoid (MMP), formerly called scarring pemphigoid, is a rare type of pemphigoid, affecting the mucous membranes - in 85% of cases the mucous membranes of the oral cavity are affected - and only in 20-30% of cases - the skin [9].

2.2.2. Clinical Picture

Typical lesions are subepidermal tense blisters, on erythema and urticarial skin and on normal looking skin. They are most often located on the skin of the trunk and the flexural surfaces of the limbs. Mucous membranes are affected in 10-20% of cases and most often affect the oral cavity, where the disease is dominated by painful erosions. The lesions are usually accompanied by skin itching. It is emphasized that in each case of severe pruritus in elderly patients, the diagnosis of pemphigoid should be considered. In mucous membrane pemphigoid, lesions may subside with scarring. Atypical clinical forms of pemphigoid are not the subject of this study [10].

2.2.3. Diagnosis and Pharmacological Treatment

Pemphigoid is diagnosed based on the clinical picture, histopathological examination and immunopathological test results. Histopathological examination reveals a subepidermal blister and an inflammatory infiltrate with a predominance of eosinophils located around blood vessels. The basis of diagnosis is the detection of linear deposits of IgG and/or complement component C3 along the basement membrane in direct immunopathological examination. Often, indirect immunopathological examination, i.e. in the patient's serum, detects circulating antibodies against pemphigoid typical antigens BP180, BP320 or other antigens. The concentration of antibodies does not correlate with the activity or severity of the disease. The first-line treatment is strong local glucocorticoids (clobetasol propionate), which are used a few months after the lesions disappear. Systemic glucocorticoids are also effective in the treatment of this disease, however, due to the older age of patients, many comorbidities and increased exposure to the development of side effects, experts advise against this method of treatment as the first line. Other drugs used in the treatment of pemphigoid include methotrexate, tetracyclines, azathioprine, mycophenolate mofetil, cyclophosphamide and dapsone [11,12].

2.3. Dermatitis Herpetiformis (During's Diseases)

2.3.1. Epidemiology and Etiopathogenesis

The prevalence is estimated at 1.2-75.3/100,000, while the incidence of Duhring's disease is 0.4-3.5/100,000/year. It decreases by 4% annually, which may be due to the preventive effect of a gluten-

 doi:10.20944/preprints202407.2187.v1

free diet in patients with gluten-dependent enteropathy. The disease affects men slightly more often than women, and the onset of changes usually occurs in the 4th or 5th decade of life; it may run in families, more often in siblings than in parents and children. In approximately 90% of patients, features of gluten-dependent enteropathy are detected in histopathological sections from the mucosa of the small intestine. Both genetic factors - most patients have HLA DQ2 and HLA DQ8 - and environmental factors play a role in the etiopathogenesis of the disease. The main autoantigen is tissue transglutaminase. In people with a genetic predisposition, the immune response is stimulated and the synthesis of specific IgA directed against tissue transglutaminase is triggered, and the autoimmune process is extended to include IgA recognition of epidermal transglutaminase antigens. In histopathology and immunopathology, we see this phenomenon as complexes consisting of IgA and tissue transglutaminase in the apex of dermal papillae. This mechanism leads to the development of changes typical of dermatitis herpetiformis. It is worth emphasizing that a diet rich in gluten increases the immune reaction against tissue transglutaminase. It has been observed that the use of a gluten-free diet in Duhring's disease reduces IgA synthesis by 50% after 2 months of its use [13,14].

2.3.2. Clinical Picture

Polymorphic skin lesions in the form of vesicles, blisters, exudative papules, urticarial eruptions, erosions covered with crusts, often with a herpetic pattern, are symmetrical and most often affect the skin of the elbows and knees (90% of cases) and the skin of the buttocks and the lumbosacral area. The skin in other areas may also be affected. Mucosal involvement is very rare. The skin lesions are accompanied by severe itching and burning of the skin. The autoimmune process towards skin transglutaminases is usually accompanied by clinically asymptomatic or mildly symptomatic gluten-dependent enteropathy. Fewer than 10% of patients have malabsorption syndrome, flatulence or diarrhea. Intensification of skin lesions is also observed after exposure to iodine, both taken with the diet and applied externally [15].

2.3.3. Diagnosis, Pharmacological Treatment, and Diet Therapy

The diagnosis of dermatitis herpetiformis is based on the characteristic clinical picture of the lesions, confirmed by immunological tests and possibly by histopathological examination. The diagnosis is based on the detection of granular IgA deposits in skin papillae during direct immunofluorescence examination of a section of unaffected skin near the lesions. The gold standard of treatment is gluten free diet and dapsone. Symptoms such as itching and burning of the skin disappear spectacularly after 24-48 hours of using the drug. Then the skin lesions slowly disappear. Dapsone does not affect intestinal changes. At the same time as the introduction of dapsone, a gluten-free diet should be implemented, which affects both skin and intestinal lesions, and its effects are visible after a few months, at least after 3-6 months. A gluten-free diet also reduces the risk of developing gastrointestinal lymphomas in patients with dermatitis herpetiformis. Exacerbation of the disease is also observed after exposure to iodine. Patients should avoid iodine in food (sea fish, seafood, sea algae, iodized salt, mineral waters containing iodine) and external exposure, i.e. disinfectants with iodine or iodine in seaside air [16,17].

2.4. Epidermolysis Bullosa Aqusita

2.4.1. Epidemiology and Etiopathogenesis

It is an autoimmune subepidermal bullous disease in which the autoimmunity process is directed against epitopes of collagen VII, which is a protein that forms anchoring fibers connecting the basement membrane with the dermis. The incidence of epidermolysis bullosa aqusita. (EBA) is estimated at 0.25/1,000,000 and occurs in both children and adults of all ages. Inflammatory bowel disease is diagnosed in 25% of patients. Adult patients may have comorbid cancer [18].

2.4.2. Clinical Picture

 doi:10.20944/preprints202407.2187.v1

The disease affects the skin and mucous membranes. Usually, blisters are located on the extensor parts of the limbs, which are susceptible to mechanical injuries. The lesions heal leaving milia and atrophic scars. Mucous membranes are dominated by erosions after rupture blisters, especially in the mouth, mucous membranes of the eyes and genitals [19].

2.4.3. Diagnosis and Pharmacotherapy

The diagnosis is made based on the clinical picture and additional tests. Direct immunofluorescence examination reveals IgG deposits arranged linearly along the basement membrane. Indirect immunofluorescence tests detect the presence of circulating IgG antibodies that bind to the basement membrane. To differentiate it from pemphigoid, a skin split test is performed. In pemphigoid, immune deposits are located in the roof of the artificially created blister, while in EBA, they are located in the dermal part of the blister. The histopathological results is inconclusive and may resemble pemphigoid. Pharmacotherapy is based on systemic glucocorticoids, sometimes in combination with sulfones. Other options include colchicine, immunosuppressive drugs or immunoglobulin infusions [19].

3. The Role of Nutrition in Autoimmune Bullous Diseases

3.1. Dietary Factors

There is a lot of scientific evidence confirming the influence of nutritional factors and mineral deficiencies on the development of pemphigus [20–25]. In one analysis, 46.2% of pemphigus patients mentioned food as a possible trigger for their disease [24]. Dietary factors that exacerbate, precipitate and/or relapse the disease include: thiols and onion vegetables (Allium) (garlic, onion, leek, chives); phenols (mango, pistachio, red pepper, black pepper, cinnamon, fennel); tannins (coffee, tea, raspberry, guarana, cranberry, avocado, wild strawberry); tannins (cocoa, vanillin, tea, tree bark); phycocyanin (cryptophytes, red algae, cyanobacteria); isosulfurcyanin (white and black mustard, horseradish, nasturtium); all trans-retinoic acids; cinnamic acid (tomato, orange, grapefruit); walnut antigens; fast food; and herbs (algae - Spirulina platensis, horsetail herb, rosehip, echinacea, ginseng) [26,27].

3.1.1. Thiols and Bulb Vegetables (Allium)

Thiols are organic compounds that contain a sulfhydryl functional group (-SH). Allium vegetables contain both thiol and disulfide groups. These compounds play a role in the formation of blisters, especially in patients with a genetic predisposition. Thiols are found in food (garlic, onion, leek, chives), medicines (captopril, penicillamine) and cosmetic products. Sulfhydryl radicals inhibit the enzymes that aggregate keratinocytes and activate the enzymes that disaggregate them. Additionally, thiols form thiol-cysteine bonds instead of cysteine-cysteine bonds, which further disturbs cell adhesion. According to the latest scientific research, 15% of patients reported garlic as a trigger for pemphigus. Many patients declared that their symptoms were exacerbated and/or triggered after consuming leeks and garlic, and they declared that their symptoms disappeared after eliminating garlic, onions and leeks from their diet [26,28–30].

3.1.2. Phenols

Phenols are organic compounds whose hydroxyl group is attached to a carbon that is part of the aromatic ring. This group of compounds includes free phenols (which are often components of essential oils), phenolic glycosides and phenyl acids (which are components of plants). These compounds are found in the following foods: pistachio, cinnamon, mango, red pepper, black pepper, thymol (essential oil of thyme), eugenol (essential oil of clove flower buds), aspartame, cinnamon bark oil, pea seeds, rosmarinic acid, cynarin (artichoke), allspice, fennel, curcumin (Curcuma longa root), arbutin (viburnum leaves, pear leaves, marjoram herb), mace, milk. Studies have shown that keratinocytes exposed to phenol release IL-1α and TNFα, which increase complement and protease

 doi:10.20944/preprints202407.2187.v1

synthesis, thereby contributing to inflammation and acantholysis in tissue samples from pemphigus vulgaris patients and mice. These compounds are involved in the induction of pemphigus in genetically predisposed patients. However, it should be strongly emphasized that the elimination of phenolic compounds from the diet absolutely does not allow any reduction in the dose of systemic glucocorticoids in these patients. Phenols are also found in cleaning products. A case of pemphigus vulgaris has been described in a woman after contact with cleaning products containing phenols [1,31].

3.1.3. Tannic Acid

Tannic acids are a group of organic chemical compounds composed of D-glucose and gallic acid. They are found in coffee, tea, eggplant, cassava, cherries, blackberries (leaves), cranberries, ginger, avocados, oak bark, blueberries, wild strawberries, sage, willow bark, walnuts, cashew nuts, rosemary, ground pepper (betel).), cassava and mango. After incubation of keratinocyte cultures with various concentrations of gallic acid, a key role of the local immune response was found. Tannins play a special role in the case of endemic pemphigus. The presence of tannins in the food and living environment of people in the Amazon basin, India and Brazil is suspected, e.g. due to the exceptionally high consumption of Indian tea, water from the Amazon basin and guarana - popular in South America. These compounds are involved in the induction of pemphigus, especially in genetically predisposed patients. Importantly, eliminating tannins from the diet absolutely does not allow for reducing the dose of systemic glucocorticoids in these patients [32–36].

3.1.4. Tannins

Tannins are polyphenolic compounds naturally found in tree bark, plants, black pepper, cherries, blueberries, mangoes, cashews, tea, vanillin and cocoa. They are capable of forming complexes with metal ions. Tannins are also believed to have antioxidant properties. Research shows that patients who consume large amounts of tannins in their diet also have higher concentrations of them in their skin. These communities are suspected to be disproportionately affected by the disease due to their proximity to rivers with high tannins in their water systems and diet. Additionally, the diagnosis rate of pemphigus vulgaris is high in India, which may be related to the consumption of large amounts of tea and betel nut [37].

3.1.5. Phycocyanin

Phycocyanin is a blue pigment found in cryptophytes, cyanobacteria and red algae. It has fluorescent and antioxidant properties. This compound is responsible for the induction of pemphigus, especially in genetically predisposed patients. We report the case of a 57-year-old man with pemphigus vulgaris whose symptoms worsened after consuming a diet containing phycocyanin. However, the elimination of phycocyanin from the diet does not allow for any modification of the dose of systemic glucocorticoids in these patients [37].

3.1.6. Isosulfurcyanates

Isosulfurcyanates (so-called mustard oils) are compounds belonging to glucosylates that contain glycosidic sulfur links. They are generally unstable compounds - liquid, oily. They are found in white (mustard) and black mustard, as well as in horseradish and nasturtium. They are responsible for the induction of pemphigus, especially in genetically predisposed patients. Despite reports regarding the association of isosulfurcyanine with causing blistering lesions on the oral mucosa, there are no confirmed studies on this subject so far. As in the case of tannins, phenols and phycocyanin, eliminating isosulfurcyanates from the diet does not allow for reducing the dose of systemic glucocorticoids in patients [37].

3.1.7. All Trans-Retinoic Acids

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The vitamin A metabolite, retinoic acid, has been shown to modulate the immune system by influencing the proliferation, differentiation and apoptosis of immune cells. These metabolites may play a role in modulating pemphigus by causing Th17 cell depletion while stabilizing regulatory T cells. This relationship is further complicated by the fact that all trans-retinoic acids shift the balance of the Th1 to Th2 ratio towards Th2, which is known to be elevated in patients with pemphigus [38].

3.1.8. Cinnamic Acid

Cinnamic acid is an organic chemical compound containing a double bond and a benzoic ring. It is found in candied fruit, tomatoes, oranges and grapefruits. In one study in which pemphigus patients were asked to list possible triggers, the most frequently mentioned food-related trigger was tomato (23.1%), which is high in cinnamic acid [39].

3.1.9. Walnut Antigens

Walnut antigens introduced into the body cause an immune reaction consisting in the proliferation of lymphocytes and the formation of specific antibodies. Research suggests that exposure to walnut antigen through gastrointestinal epithelial cells may activate B cells in individuals genetically predisposed to pemphigus vulgaris through a hit-and-run mechanism. By this mechanism, cross-reactivity between the infectious antigen and the self-antigen may lead to a long-lasting immune response, even after the pathogen has been cleared, because the continued presence of the self-antigen will continually drive the generation of autoantibodies and the development (as well as perpetuation and/or exacerbation) of the disease [40,41].

3.1.10. Fast-Foods

Fast food is a type of highly processed food, prepared quickly and eaten hot, usually cheap. These include products such as pizza, hamburgers, fries, etc. These foods may influence the development of pemphigus. However, the pathomechanism is not fully known and requires further research [1].

3.2. Vitamins and Minerals

Important vitamins and minerals in the pathogenesis and treatment of pemphigus are vitamin D, vitamin B3, calcium, selenium, copper, zinc, and potassium [23,42–51].

3.2.1. Vitamin D

Vitamin D includes vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). It is of fundamental importance in the regulation of calcium and phosphate metabolism and the metabolism of bone tissue. The most important sources of vitamin D for humans include its endogenous synthesis (approx. 80%). This vitamin is found mainly in products of animal origin (oils, fatty fish, eggs). There are several hypothetical roles of vitamin D in the pathogenesis of pemphigus vulgaris. In vitro studies have shown that vitamin D increases beta cell apoptosis while reducing their proliferation and increasing the number and function of regulatory T cells. Vitamin D has also been shown to protect keratinocytes from several apoptosis pathways. It was found that patients with pemphigus vulgaris had lower vitamin D levels, regardless of body mass index, age and sun exposure. Its supplementation is important in the case of pemphigus treatment with the use of chronic glucocorticosteroids therapy and during long-term treatment of pemphigus with the use of immunosuppressive drugs [42–48].

3.2.2. Vitamin B_3

Vitamin B3 is the general name for two compounds: niacin and nicotinamide. It acts as a precursor for NADP and NAD coenzymes involved in oxidation and reduction processes. It is commonly found in food, and its main sources are: meat (turkey, chicken), liver, meat products, fish,

 doi:10.20944/preprints202407.2187.v1

nuts, whole grain products, milk, cheese and eggs. Research into autoimmune bullous diseases has shown that nicotinamide in combination with minocycline is effective in the treatment of bullous pemphigus. These were observations carried out in a 76-year-old woman with comorbidities and a 46-year-old patient with esophageal involvement [49,50]

3.2.3. Calcium

Calcium (Ca) is one of the basic building materials for bones and teeth. Additionally, it is involved in muscle contractility, conduction of nerve impulses, hormonal regulation and activation of some enzymes. The best source of calcium is milk and its products. Significant amounts of this ingredient also contain products of plant origin, such as parsley leaves, kale or spinach - however, calcium from these products is not as well absorbed compared to milk and its products. Calcium supplementation is recommended at the beginning of glucocorticosteroid treatment to prevent secondary osteoporosis. In the case of pemphigus treatment with chronic glucocorticosteroid therapy, supplementation of this mineral is recommended at a dose of 1000-1200 mg [51,52].

3.2.4. Selenium, Zinc, and Cooper

Selenium (Se) takes part in the metabolic processes of the cell and protects against free radicals. Products rich in selenium include offal (especially kidneys), seafood (fish and crustaceans) and some vegetables (mushrooms, garlic, dry legumes). In the human body, zinc (Zn) has structural, regulatory and catalytic functions. It takes part in the metabolism of carbohydrates, fats and proteins, and also influences the processes of memory and learning. It is found in liver, meat, brown bread, rennet cheese, eggs and buckwheat. Copper (Cu) is a component of many enzymes, it is involved in the metabolism of oxygen and the metabolism of iron in the body. Products rich in copper include wheat bran, offal (especially liver), sunflower seeds, nuts, and cocoa. It has been shown that patients with pemphigus vulgaris have lower serum concentrations of copper, selenium and zinc compared to healthy volunteers. It is believed that these tendencies may be caused by improper nutrition associated with painful lesions in the oral cavity or chronic inflammation. Data on this association are limited and there are no clear guidelines regarding supplementation for these nutrient deficiencies in pemphigus [52,53].

3.2.5. Potassium

Potassium (K) is involved in regulating the osmotic pressure of cells, maintaining water and electrolyte balance and the metabolism of proteins and carbohydrates. Large amounts of potassium contain nuts, seeds, dried fruits, chocolate, cocoa, vegetables, fruits, meat and cereal products. Potassium supplementation is recommended in the treatment of pemphigus in people using chronic glucocorticoid therapy. The dose should be adjusted based on serum electrolyte levels routinely performed during glucocorticoid therapy [52].

3.3. The Role of Diets

According to the International Pemphigus & Pemphigoid Foundation IPPF, there is no single diet that will help treat ABM. However, there are certain recommendations regarding products that exacerbate or alleviate the symptoms of the disease. Additionally, various types of diets have been described in the literature (including gluten-free, pulpy, or high-protein diets) that have a potential impact on the development or support the remission of the disease [54,55].

According to the IPPF, products that are bothersome for patients include: citrus fruits, sour fruits, bagels, garlic, chips, barbecue/cocktail sauces, horseradish, red pepper, onions, tomato sauces, chocolate, pickled cucumbers, tomatoes, roasted corn, pretzels, pizza. , coffee. It is recommended to rinse your mouth with water, hydrogen peroxide or a moisturizing and soothing solution during and after eating to help remove food and bacteria and accelerate healing. In order to prevent malnutrition, it is recommended to eat a variety of foods every day, take vitamin supplements and measure body weight weekly - and if weight loss occurs, increase the supply of kilocalories and protein. In the

 doi:10.20944/preprints202407.2187.v1

course of pemphigus and other autoimmune blistering diseases, diet plays an important role. It is classified as a treatment-supporting therapy, the main goals of which include: maintaining the patient's proper nutritional status; elimination of products and dishes that initiate or exacerbate the disease process, and introduction of products that have a positive impact on the course of the disease [55].

There are many factors that influence the nutrition (including nutritional status and diet) of patients with autoimmune bullous diseases. These include: i) A number of dietary factors that are believed to play an important role in the onset, progression, exacerbation and treatment of this disease, ii) Increased catabolism due to epidermal detachment and protein loss; iii) Hydroelectrolytic imbalance caused by fluid loss through skin lesions; and iv) The need for vitamin D and calcium supplementation in the prevention of secondary osteoporosis as a result of long-term glucocorticoid therapy.

In patients who have difficulty swallowing or have complications after glucocorticosteroids therapy, it is recommended to establish an appropriate diet with a dietitian. The diet most commonly used in the treatment of pemphigus and other autoimmune blistering diseases are soft diet, diet rich in protein, diet rich in calcium, DASH diet (Dietary Approaches to Stop Hypertension), mediterranean diet, and gluten-free diet [39,56].

3.3.1. Soft Diet

The pulp diet is similar to the easily digestible diet in terms of energy value and product selection but differs in consistency. It is recommended for diseases of the oral cavity and/or esophagus, for people who have problems with biting and/or swallowing. Its goal is to provide the patient with all the necessary nutrients and, as a result, prevent malnutrition. In pemphigus, due to the occurrence of blister-like changes with the formation of erosions on the mucous membranes of the mouth and/or throat, patients often have problems with biting and/or swallowing. This diet works well for these patients because the changed consistency makes it easier to eat. Dishes and products are served in a form that does not require biting. A very important ingredient is animal protein, B vitamins, vitamin C and minerals. The main thermal treatment is cooking so as not to irritate the affected areas. Creamy and puree soups are widely used in this diet. Recommended products include: crustless bread, soft, soaked in milk or tea, crumbled; minced meats cooked or prepared from minced meat; vegetables and fruits in raw form in the form of juices or cooked and crushed. It is recommended to eat 4 or 5 meals a day. Permitted spices are: lemon balm, dill, cinnamon, marjoram, cloves, vanilla. Assumptions for a pulpy diet include total protein (16% of the total dietary energy requirement, E), fats (30%E) and carbohydrates (54%E) [25,54].

3.3.2. High-Protein Diet

The aim of a high-protein diet is to provide the appropriate amount of protein for the construction and reconstruction of body tissues. It is characterized by an increased supply of protein (15-20%E) with a limited intake of carbohydrates (below 40%E). When used in pemphigus, the protein supply is 2-3g/kg body weight/day. Most (2/3) of this macronutrient should come from animal products, such as: milk, cottage cheese, lean meats, lean meats, and eggs. You should limit your intake of salt, salty snacks and processed foods [54].

A high protein supply in pemphigus is important due to the increased catabolism caused by epidermal detachment and potentially associated cancer. A high-protein diet is used in severe cases of pemphigus, as well as in the treatment of pemphigus with chronic glucocorticosteroids therapy. Its aim is to minimize protein loss and accelerate the healing of skin and mucosal lesions. In most patients, insertion of a nasogastric tube is required because erosions of the mucosa make oral feeding difficult. In patients able to eat independently, intermittent tube feeding is used, also at night. A nasogastric tube and possibly venous access are also necessary to correct fluid and electrolyte imbalances. Additionally, calcium and vitamin D supplementation is important to prevent secondary osteoporosis [54].

 doi:10.20944/preprints202407.2187.v1

3.3.3. High-Calcium Diet

A high-calcium diet is characterized by an increased supply of calcium. Most of this mineral is found in milk and its products. It is mainly used in the osteoporosis that already accompanies pemphigus and in chronic glucocorticosteroids therapy. A calcium intake of 1000-1200 mg is recommended, which is also intended to prevent secondary osteoporosis associated with the use of glucocorticoids [54].

3.3.4. The DASH Diet

The DASH diet (Dietary Approaches to Stop Hypertension) has a beneficial effect on blood pressure and reduces the risk of coronary heart disease and stroke. It involves limiting the consumption of: salt (less than 2.3 g of sodium/day), highly processed foods, sugar and fats rich in saturated fatty acids; and increasing the consumption of vegetables, fish and fruit, as well as the supply of potassium, calcium, magnesium and dietary fiber, and ensuring the right amount of protein. In autoimmune bullous diseases, this diet is used in chronic glucocorticoid therapy [54,56].

3.3.5. The Mediterranean Diet

It is characterized by a low consumption of animal fats and a high consumption of plant products. In this diet, it is recommended to eat fresh fruit, bread, pasta, groats that are as little processed as possible, as well as whole-grain rice, yogurt, fish, low-fat dairy products, and nuts. The consumption of meat, eggs, yellow and fromage cheeses and sugar is limited. Similarly, to the DASH diet, it is used in autoimmune bullous diseases in which glucocorticoids are used chronically [57].

3.3.6. Gluten-Free Diet

In dermatitis herpetiformis, it is advisable to follow a gluten-free diet and eliminate iodine from the diet (fish and seafood, iodized table salt, sea algae, mineral water containing iodine). Well-controlled patients with Duhring's disease treated by a dermatologist, gastroenterologist, and dietitian have an excellent prognosis. When recommending a diet low in iodine, remember that it is necessary for the body's metabolic processes, especially those regulated by thyroid hormones, and is very important for the proper growth and development of children. The mechanism by which iodine compounds intensify skin lesions is not sufficiently understood. Patients should avoid staying in coastal areas where there is a high content of iodine compounds. Taking mineral and vitamin preparations containing iodine compounds may also worsen the symptoms of the disease. Patients with dermatitis herpetiformis are advised to avoid all products containing gluten (which is a mixture of proteins: gliadin, gluten, secalin, avenin and hordein), made from cereals, including wheat (also spelt, emmer, einkorn, durum wheat), barley, rye and malt. Gluten may also be found in food products from other groups to which ingredients derived from gluten-free cereals in any form have been added (e.g. wheat fiber, wheat starch syrup, pure gluten, breadcrumbs, etc.). These ingredients can be added to popular cold meats (lunch meat, sausages), delicatessen products, some sweets, dairy products, food concentrates, spices, canned goods, ready-made sauces, desserts, etc. When buying ready-made products, always check their composition on the labels. Gluten-free products are marked with a certificate number and often with the Crossed Ear symbol. This mark on certified gluten-free products is both an international and Polish symbol of safe gluten-free food. Certification means that the product is made from safe raw materials and regularly tested for gluten content [54].

It is worth noting that DH patients can consume pure oat products. Recent studies have shown that oats are not only safe, but in the long run they can improve your quality of life and eliminate any gastrointestinal symptoms. However, sufferers should exercise caution because most store-bought oat products are usually contaminated with gluten, so it is recommended to avoid oats or products containing this grain. A good solution is to buy certified oat products. Examples of gluten-free foods that are safe to eat include rice, corn, potatoes, vegetables and others listed in Table 1. When preparing meals with gluten-free products at home, be careful not to cross-contaminate them with gluten, e.g.

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by using the same cutting board for cutting gluten-free and regular bread or the same spoon for gluten-free sauce thickened with wheat flour [58].

Adherence, unfortunately, is difficult for patients in practice because it requires meticulous monitoring of food labels and consumption, can be costly and inconvenient, and is socially limiting. Studies from many centers confirm that compliance with the diet depends to the greatest extent on patients' knowledge about the disease and its treatment. Dietitians and support groups are helpful in dealing with compliance challenges and pinpointing hidden sources of gluten. Patients can also benefit from the support of various associations, e.g. the Polish Association of People with Celiac Disease and on a Gluten-Free Diet [https://celiakia.pl]. Communication with the patient and family should emphasize the importance of following an appropriate diet even in the absence of symptoms.

Over the past two decades, several studies have assessed the possibility of long-term remission of Duhring's disease in 10–20% of cases, which has suggested the possibility of discontinuing the gluten-free diet in well-controlled patients. However, it was recently shown that 95% of patients who were well controlled on long-term gluten-free diet therapy relapsed after gluten challenge. Therefore, for now, it is recommended to use it throughout life. It is also recommended to constantly monitor the patient for compliance with dietary recommendations and the risk of nutritional deficiencies resulting from the use of the elimination diet [13].

A gluten-free diet affects both skin and intestinal changes. Please remember that its effects are only noticeable after many months of use (minimum 6 months). Its scrupulous use can even protect many patients from the use of pharmacotherapy. It is worth emphasizing the observation that the use of a gluten-free diet in patients with dermatitis herpetiformis also reduces the risk of developing gastrointestinal lymphomas [58].

3.4. Dietary Management in Autoimmune Bullous Diseases Treated with Chronic Glucocorticosteroid Therapy

The advent of corticosteroids in the early 1950s revolutionized the prognosis for many autoimmune bullous diseases and led to a drastic decline in patient mortality (especially in patients with pemphigoid vulgaris). GCS are the most commonly used drugs in skin diseases. Many patients with autoimmune bullous diseases use glucocorticosteroid therapy chronically, i.e. for more than 3 months. The most commonly used glucocorticoids include prednisone, prednisolone and dexamethasone [59]. There are many beneficial aspects of using glucocorticoids in the treatment of autoimmune bullous diseases, the most important of which is the reduction of mortality among these patients. However, GKS also have a negative effect by impaired calcium absorption from the gastrointestinal tract, increased loss of calcium in urine, and inhibition of the synthesis of 25-hydroxycholecalciferol in the liver and 1,25-dihydroxycholecalciferol in the kidneys, which ultimately leads to osteopenia and/or osteoporosis [60].

However, it must be strongly emphasized that the choice between life and side effects that can be lived with should not be shifted towards increasing the risk of death. Osteoporosis is a chronic, progressive disease manifested by low bone mass and degradation of the microarchitecture of bone tissue. This disease leads to weakening of bone strength, which consequently increases the risk of fractures. Osteopenia is the early stage of osteoporosis. Studies indicate a high percentage of patients with osteopenia and osteoporosis in pemphigus treated with glucocorticoids. According to one of them, this percentage was as high as 41.9%. It is estimated that significant bone loss and bone fractures affect 30-50% of patients with pemphigus. Within 3-6 months of therapy, this risk increases dramatically. Moreover, patients often struggle with cardiovascular diseases and insulin resistance. Therefore, in the case of long-term glucocorticosteroid therapy, in addition to lifestyle modeling related to stopping smoking and drinking alcohol, it is recommended (depending on the complications related to the glucocorticosteroid therapy) a diet: high-protein, high-calcium, DASH and Mediterranean, or a combination of them. It is also recommended to supplement calcium, vitamin D and potassium. The general scheme of dietary management when using chronic glucocorticoid therapy in autoimmune bullous diseases is presented on Figure 1. It is important to outline that under no circumstances should dietary therapy be used to modify the dose of

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glucocorticoids taken by patients with autoimmune bullous diseases. Such action can only increase the mortality rate of patients [51,59,60].

3.5. Dietary Management and the Risk of Cardiovascular Diseases in Autoimmune Bullous Diseases

Recently, there has been a lot of interest in the relationship between diet and the risk of developing cardiovascular diseases in patients with pemphigus. This is probably due to their high frequency in this group of patients [75]. According to one of the first studies in this area, from 2022, which assessed the impact of dietary diversity on the risk of cardiovascular diseases among 187 patients aged 18-65 with pemphigus vulgaris, no connection was clearly demonstrated between the above-mentioned factors. factors. There was no relationship between the dietary diversity index and the occurrence of obesity and glucose homeostasis disorders. However, the results of this cross-sectional study showed that the dietary diversity index may be associated with increased concentrations of total cholesterol and HDL cholesterol. However, further prospective studies are needed to confirm these observations [76]. Moreover, according to a randomized, double-blind study, the use of L-carnitine supplements in patients with pemphigus vulgaris had a beneficial effect on cystatin C, which led to favorable changes in markers of cardiovascular and bone turnover [61,62].

3.6. Herbal Supplements

The use of herbal supplements, which can improve the functioning of the immune system, has become popular among patients with dermatological diseases. However, recommending any herbal preparations to patients with autoimmune bullous diseases should be very cautious, as herbal preparations may worsen the disease The herbs that enhance the disease process in pemphigus include algae (Spirulina platensis), echinacea, and St. John's wort (Hyperitum perforatum). Algae (Spirulina platensis), have been called "super foods" due to their high protein content and their possible hypolipidemic, antioxidant and anti-inflammatory effects, has a probable impact on the induction of pemphigus vulgaris. Echinacea is a species of plant from the Asteraceae family, comes in several varieties, the most popular of which are purple coneflower and echinacea angustifolia, enhances the body's response to inflammation and infection, has a probable influence on the induction of pemphigus vulgaris. St. John's wort (Hyperitum perforatum) - a herbal medicine with a widely known photosensitizing effect and possible immunomodulatory effect, it has a probable influence on the induction of pemphigus foliaceus [63,64].

However, cassia fistula seems to have some use in the treatment of pemphigus. It is a tropical, deciduous, green tree from India, with an upright and slender trunk and small buttresses. C. fistula fruit oil contains lupeol, anthraquinone compounds such as rhein and flavonoids. It is believed that this herb may be a recommended botanical therapeutic support in the treatment of erosions in pemphigus vulgaris [65].

3.7. The Role of Dietetician in Autoimmune Bullous Diseases

A dietitian plays an important role in the interdisciplinary team caring for a patient with autoimmune bullous disease. According to the consensus of the Polish Society of Dermatology from 2014, dietary consultation is considered a supportive treatment for pemphigus and other autoimmune skin diseases, especially dermatitis herpetiformis. It is especially recommended for patients with swallowing difficulties and complications after glucocorticosteroid therapy. The main tasks of a dietitian include: conducting a nutritional interview with the patient and assessing the nutritional status (anthropometric tests); learning about the individual varieties and clinical subtypes of pemphigus and the risk factors associated with them in order to include an appropriate diet; locating disease symptoms and their spread (e.g. skin lesions, erosions in the oral cavity); patient education regarding nutritional treatment for his disease; own education on autoimmune bullous diseases, including pemphigus and especially dermatitis herpetiformis (Duhring's disease); and monitoring the patient's health condition [7].

 doi:10.20944/preprints202407.2187.v1

The aim of the dietary consultation is to ensure the patient's appropriate nutritional status (including the prevention of malnutrition), maintain appropriate body weight by implementing appropriate nutritional treatment, and consequently improve the quality of life of patients. When determining your diet, you should take into account: the patient's current weight and height (determination of body mass index, BMI), medications you take, current comorbidities, patient's physical activity, patient's dietary preferences, and permitted and prohibited products [54].

3.8. General Dietary Recommendations for Autoimmune Bullous Diseases, especially Pemphigus

Despite the lack of clear guidelines regarding diet in autoimmune bullous diseases, especially pemphigus, based on the available literature, general dietary recommendations can be formulated for patients regardless of the type of this disease [54]. These are lifestyle modification by eliminating the use of stimulants (alcohol, cigarettes) and increasing physical activity; limiting or eliminating the consumption of products and foods rich in compounds that are known to cause or worsen the symptoms of pemphigus, such as thiols, phenols, tannins, etc., these compounds are often found in foods, drugs and cosmetic products; establishing an appropriate diet with a dietitian depending on the patient's health condition, clinical symptoms and risk factors related to the use of chronic glucocorticosteroid therapy (particular importance is attached to a gluten-free diet in dermatitis herpetiformis and a diet used in swallowing disorders in other autoimmune bullous diseases); appropriate supplementation of vitamins, minerals and L-carnitine (especially in the case of chronic glucocorticosteroid therapy); drawing attention to the usefulness and side effects of herbal supplements for patients with pemphigus and other autoimmune blistering diseases (it is important, however, not to use them as replacements for treatment - the educational role of a dietitian is crucial); monitoring the health condition as well as providing the patient with constant dietary control (especially for patients with severe pemphigus); as well as interdisciplinary approach to treatment.

4. Support Groups

In Poland, there are currently no support groups for pemphigus patients and their families. Patients should be encouraged to create them and cooperate with groups operating in the USA and Western Europe, such as: Pemphigus Vulgaris Network (www.pemphigus.org.uk), Pemphigus-Pemphigoid-France (www.pemphigus.asso.fr) or International Pemphigus and Pemphigoid Foundation (www.pemphigus.org) [55,66,67].

Patients with Duhring's disease can be advised to contact and read the information available on the website of the Polish Association of People with Celiac Disease and the Gluten-Free Diet (www.celiakia.pl) [68].

5. Conclusions

The relationship between nutrition and AIBDs is multifaceted. The literature mentions various food products and food ingredients acting as disease modifiers. Research on the use of a gluten-free diet in dermatitis herpetiformis is confirmed in the literature beyond any doubt. Research on the effects of garlic and the thiols and phenols that may cause pemphigus is well established, but there are many other ingredients that do not have enough scientific support to recommend avoiding them. Nevertheless, based on the available literature, general dietary recommendations for patients and guidelines for dietitians can be formulated to support the treatment process, which can be particularly fruitful if an interdisciplinary approach is used. However, further high-quality research is needed to more precisely define the relationships between nutrients and nutrition and blistering diseases.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org, Figure S1: title; Table S1: title; Video S1: title.

Author Contributions: Conceptualization, A.A.K and A.C.S.; writing—original draft preparation, A.K.K; writing—review and editing, A.C.S, A.Z., and A.Z.J.; supervision, A.C.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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