

Dietary and Nutritional Strategies for Chronic Spontaneous Urticaria: Mechanisms, Clinical Evidence, and Individualized Management

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Abstract. Chronic spontaneous urticaria (CSU) is a common form of prolonged, relapsing itching of the skin. At present, most of the treatment methods are non-sedating second-generation H1 antihistamines. Although some of these drugs are effective for some patients, their general symptom-alleviation rates are relatively low. Some of the refractory patients may choose the expensive option of omalizumab, but most patients are still not cured. Therefore, a safe, economical and convenient-to-implement method of auxiliary intervention needs to be selected. Dietary nutrition is a non-pharmacological method that has high patient compliance and can regulate all links in the pathogenesis of CSU, such as histamine metabolism, gut microbiota and immune system. This paper systematically reviews the mechanism, clinical evidence and application basis of various dietary strategies: the adjunctive therapy and pseudo-allergen avoidance diets can only serve as short-term dietary adjuvant strategies, and are recommended for patients with clearly identified triggers of CSU. Vitamin D supplementation can inhibit mast cell degranulation and promote a T helper 2 (Th2) immune shift. Probiotics and diamine oxidase can repair the intestinal barrier and reduce the impact of exogenous histamine on the body. This review focuses on CSU, explores the mechanisms of action for all types of dietary and nutritional approaches in CSU, compares their clinical values, and offers a reference for personalised dietary-nutritional treatment plans for patients.

Keywords: Chronic spontaneous urticaria (CSU), Diet and nutrition, Low-histamine diet, Vitamin D, Gut microbiota

1. Introduction

Chronic spontaneous urticaria (CSU) is a relatively common disease that does not respond well to treatment for more than six weeks and presents as recurrent spontaneous itchy wheals and angioedema. Based on the survey, the proportion of the Chinese population with chronic urticaria (CU) is 2.6%, and more than half of these CU patients have chronic spontaneous urticaria (CSU). Although it is not fatal, the disease will interfere with one's sleep and mood, etc. Some patients will be anxious or depressed because of their illness.

The latest relevant guidelines for CSU at home and abroad have unanimously recommended non-sedating second-generation H1 antihistamines as the first-line treatment for CSU. However, fewer than half of the patients' symptoms can be relieved by taking a standard dose of H1 antihistamines in practice. Even after four increases in dosage, 10%-50% of the patients still have not shown significant improvement in their health.

Omalizumab is an injectable drug that can be used to treat refractory diseases, but it is relatively expensive. Therefore, it is not suitable for all patients, and even when employed, complete remission is not guaranteed [1]. Diet and nutrition that are associated with good patient adherence are gradually gaining attention in the clinical and research communities for their application value in the auxiliary diagnosis and treatment of CSU [1-3].

There are many different clinical studies on the various types of dietary intervention, and their results are also not always in agreement. With the progress of nutritional immunology and evidence-based medicine, the function of food in the development of CSU has changed. It is no longer considered only an allergen, but rather a modulator of the immune system and thus relevant to all eating habits. CSU is used as the starting point of this review to examine the role of diet and nutrition in the auxiliary treatment of CSU, explore the level of evidence and clinical application value for different dietary strategies, and provide a reference for personalised dietary management of patients.

2. Mechanisms linking diet and CSU

Many patients with CSU have reported in the clinic that some substances cause symptoms of increased itching. Therefore, many doctors have added dietary management to their overall treatment plans for CSU and, based on the identification and avoidance of certain trigger foods, have regulated symptoms. However, with the development of nutritional immunology and evidence-based medicine, the research focus of diet in CSU has shifted from "identifying allergenic foods" to "the immunomodulatory effects of overall dietary patterns".

2.1. A shift in focus from "identification of allergenic food" to "immunomodulatory effects of the whole dietary pattern"

Early research on the connection between diet and CSU focused mainly on the IgE-mediated food allergy hypothesis. That is to say, specific IgE antibodies in a person's body bind to particular proteins in food that are considered allergens, thereby stimulating mast cells and basophils to release inflammatory substances, and consequently manifesting as symptoms such as urticaria and pruritus. Based on the above hypothesis, most studies have focused on how to recognise and avoid food allergens such as seafood, eggs and milk.

With the development of research technology and changes in the form of research, many pieces of evidence have gradually appeared that contradict this hypothesis. A systematic review showed that the complete remission rates of a pseudo-allergen-free diet and a low-histamine diet were relatively low. Therefore, most of the symptoms of CSU patients are not alleviated by the above-mentioned diet. Clinical studies have found that many cases of food sensitivity have been ruled out as false positives by double-blind, placebo-controlled food challenge tests (DBPCFC), and thus many CSU patients do not have typical IgE-mediated food allergies. Avoiding allergenic food is not feasible for these patients, and too many general dietary restrictions may lead to malnutrition, anxiety and depression.

Because current clinical observations and basic research cannot explain the connection between diet and CSU through the avoidance of allergenic foods, dietary research on CSU has begun to break out of the traditional framework of food allergies and focused on the intrinsic link among food components, gut microbiota, the immune system, and the pathogenesis of CSU. The onset of CSU is not considered to stem from short-term exposure to individual sensitizing food triggers. It is thought that the cumulative effect of long-term dietary habits and dietary structure on the body's immune system through all sorts of indirect paths, such as histamine metabolism, gut microbiota, and chronic low-grade inflammation, eventually leads to the disease. This idea provided a new direction for the following dietary adjuvant therapy of CSU and promoted a shift from "finding sensitising foods" to "the immunomodulatory effect of the entire dietary pattern".

2.2. The mechanism of diet in CSU

2.2.1. Histamine metabolism

Histamine is a major cause of the disease in CSU, and the diet of a person can also change their histamine levels. Histamine is mainly degraded by two ways: diamine oxidase and histamine N-methyltransferase. Diamine oxidase is mainly responsible for the degradation of dietary histamine, and histamine N-methyltransferase is responsible for deactivating endogenous histamine. Histamine in the diet can be broken down and regulated by diamine oxidase in the intestine under normal circumstances, but the activity of diamine oxidase in the intestine of CSU patients is generally low. Sustained release of histamine by endogenous mast cells can cause or aggravate urticaria.

In addition to food items that increase the amount of histamine in the body directly, some other parts of the food can raise histamine indirectly via non-immune pathways. For example, food additives such as nitrates and artificial colours do not contain histamine, but can directly cause mast cell degranulation through non-IgE-mediated pathways and release inflammatory mediators such as histamine and tryptase-like enzymes. As a result, these are pseudoallergic reactions that show clinical features similar to true allergies but have a different immunological basis.

2.2.2. Gut microbiota and mucosal barrier

The gut is the largest immune organ in the body, and together with the composition of gut microbiota, the function of the mucosal barrier forms a core part of the "gut-skin axis" that affects CSU [1, 4]. A stable gut microbiota is required to maintain normal immune function, and changes in daily diet are one of the main reasons for alterations in the gut microbiota. A high-fibre, low-fat diet can help develop a rich and diverse gut microbiota. Otherwise, a diet lacking fibre and being high in fat and sugar may lead to dysbiosis. Dysbiosis of the gut damages the intestinal lining, increases its permeability, and thus allows metabolites produced by intestinal bacteria to enter the blood. These can impair the immune system's function and exacerbate the symptoms of CSU. At the same time, the intestinal mucosal immune system keeps immune tolerance to food antigens and symbiotic flora through mechanisms such as secretory IgA, antimicrobial peptides and tight junction proteins. An unhealthy diet can also weaken the barrier function. Thus, food antigens may be abnormally exposed to submucosal immune cells, leading to local and systemic inflammation, and worsening symptoms of CSU. Although there is no direct evidence to support a causal link between damage to the mucosal immune barrier and the onset of CSU at present, this mechanism has been relatively well-established in other allergic diseases, such as atopic dermatitis and food allergies.

2.2.3. Mechanism of action of vitamin D and "Fawu"

Vitamin D in CSU is a nutrient that can inhibit cell degranulation and histamine release by binding to vitamin D receptor (VDR) on the surface of mast cells, and at the same time, promote Treg cell differentiation and suppress the T helper 2 (Th2)-type inflammatory response [5,6]. Based on the above research, patients with vitamin D deficiency in CSU who received bilastine and vitamin D3 showed significant improvement in their health. Traditional Chinese Medicine can also be viewed as a kind of food that is likely to cause or worsen skin diseases. Experiments in mice have shown that the consumption of typical "Fawu", such as fish, lamb, green peppers and shiitake mushrooms, increases serum IgE levels in the model animals, reduces diamine oxidase (DAO) activity, increases the expression of Th2 cells, and inhibits the secretion of the Th1 factor IFN- γ . The two results suggest that dysregulated Th2-dominant immune response is related to CSU.

3. Clinical evidence and clinical value of various dietary strategies

At present, the main strategies for dietary intervention of CSU in clinical and research settings are restrictive diets, nutritional supplementation, microbiome modulation and dietary regulation based on traditional Chinese medicine. However, the supporting data for each diet are not the same, and their intended subjects and clinical applications also vary. The following section will systematically review and analyse the clinical evidence and clinical value of these four mainstream dietary intervention strategies for CSU.

3.1. Low-histamine diet and pseudo-allergen elimination diet

The two kinds of diets for CSU are low-histamine diets and pseudo-allergen-free diets. The first cause of CSU is likely histamine. A low-histamine diet and the elimination diet for pseudo-allergens both reduce the body's histamine levels non-immunologically. They are suitable for people with a high histamine level and food additive allergy. The low-histamine diet needs to avoid foods high in histamine for CSU patients, such as fermented products, aged cheeses and processed foods. At the same time, they should also reduce the intake of food that inhibits the metabolism of histamine in the body. A pseudo-allergen-free diet does not use food additives such as artificial colours, nitrites and benzoic acid salts. These additives are free of histamine but can still trigger mast cell degranulation and aggravate the condition [7].

Most patients are unable to achieve full control of CSU symptoms by means of these two dietary methods. Therefore, a low-histamine diet or a pseudo-allergen-free diet cannot be used as the main food intervention [8]. However, they are not completely ineffective. These two dietary interventions can reduce the frequency of episodes, the severity of pruritus, and the duration of wheals in CSU patients significantly. Podder and others, based on evidence, have determined that by using a low-histamine diet in conjunction with conventional antihistamines, the degree of symptoms for patients with treatment-resistant CSU can be reduced by 30-40%, and the effectiveness of drug therapy is improved [2].

However, the international guidelines do not directly recommend these two dietary approaches for all patients. Rather, they only suggest that they may be suitable for patients with a clear history of symptom triggers. In addition, these ways have certain defects: prolonged avoidance of certain foods can result in malnutrition, weakened immunity, and even psychological problems such as anxiety and depression. Thus, they are counterproductive.

3.2. Probiotics and diamine oxidase (DAO)

Recently, the pathogenesis of the "gut-periphery axis" has gradually begun to attract attention from the field of immunology. Probiotics and DAOs have also appeared recently as new dietary therapy options for regulating the gut microbiota and histamine metabolism, offering new directions for treating CSU [1, 4].

Disruption of the gut microbiota can lead to damage to the intestinal mucosal barrier function and increased permeability. Thus, bacterial metabolites from the gut may enter the bloodstream, cause immune system dysregulation, and thus trigger CSU. Dabaghzadeh and others randomly enrolled patients to study whether probiotics could reduce intestinal permeability in non-responsive diarrhoea after eight weeks of standard-of-care drug treatment in a clinical trial [7]. In addition to the effects of the drug alone, there were no serious side effects at this time. Exogenous histamine is mainly broken down by DAO. In some patients with CSU, the activity of DAO in the intestine is reduced. Thus, mast cells are continuously stimulated by histamine and the disease is worsened [7]. The DAO supplement is for people with low DAO levels in their bodies and those who have metabolic disorders of their exogenous metabolism, such as people with CSU. DAO supplements can help to break down histamine in the food after eating and relieve the symptoms of these patients.

DAO can only reduce exogenous histamine. It does not affect the release of endogenous histamine by mast cells in the body. Therefore, it cannot improve the basic progress of the disease. Most of the probiotic supplements are for people with digestive problems or those who have changed their diet, and DAO supplements are for individuals who cannot break down exogenous histamine in their body. Both are in the gut, and together they can be more effective.

3.3. Vitamin D

Studies have shown that vitamin D levels in patients with CSU are significantly lower than those in healthy individuals. The mean difference is -9.35 ng/mL (95% CI -12.27 to -6.44), and vitamin D levels are negatively correlated with the severity of the disease [5]. Vitamin D supplementation is required for the treatment of CSU. At present, it is a nutritional adjunct therapy with the highest level of evidence and the best safety profile. Researchers carried out a randomised double-blind placebo-controlled trial to determine whether adding a suitable amount of vitamin D3 daily to a 40mg dose of bilastine could inhibit mast cell degranulation and suppress Th2-type inflammatory reactions more effectively than 40mg of bilastine alone in patients with CSU and vitamin D deficiency. The results showed that this way improved the state of immune imbalance in these patients and had better efficacy than 40mg of bilastine alone. It will reduce the UAS7 score (7-day urticaria activity score) and relieve symptoms to a certain extent [9].

Some researchers have designated the diet at CSU as an A-level recommendation based on the evidence. Vitamin D supplements have not shown any severe side effects in other studies of patients with CSU, and it has been widely accepted as safe. Among the current main ways to modify the diet, adding vitamin D is economically feasible, safe and convenient.

3.4. Traditional Chinese medicine "Fawu"

Traditional Chinese Medicine is a particular system of treating diseases in China. "Fawu" refers to a type of food that can trigger or worsen skin diseases, such as fish, mutton, green peppers and mushrooms. In terms of Traditional Chinese Medicine, chronic urticaria is known as "yin zhen", and it is believed to be caused by blood deficiency and wind-dryness. Thus, treatment aims to regulate

Qi and blood, tonify the blood, promote blood circulation, soften the Liver, nourish the Kidneys, clear heat, dispel wind, and relieve itching [10, 11].

A diet containing "Fawu" increases serum IgE, histamine and splenic Th2 cytokine levels in mice with a CSU model, inhibits the secretion of Th1 molecules, reduces DAO activity, and thus amplifies the skin inflammatory response and worsens CSU symptoms. Different "Fawu" have different effects. Fish, lamb and green peppers are relatively effective, while shiitake mushrooms are relatively less so. Trigger foods are not only "allergic foods" but can also exacerbate the symptoms of Chronic Spontaneous Urticaria (CSU) via multiple paths, such as immune system disruption, impaired histamine decomposition, and alterations in the intestinal environment. Thus, the concept of whole-body dietary modification has been effectively validated [10].

Currently, this experiment only uses animals and has not yet been applied to humans. At present, this conclusion can only offer advice for patients with CSU. In short, the theory of "Fawu" in traditional Chinese medicine has achieved some initial results at CSU. It has many advantages in the system of traditional Chinese medicine and is likely to be a good research object. However, there is no supporting medical evidence, such as clinical trials. In the future, standardised clinical trials will be carried out to provide theoretical support for the development of new dietary-treatment methods based on traditional Chinese medicine.

4. Holistic dietary patterns and individualised nutrition management

With the deepening study of diet and CSU, dietary therapy has moved beyond the previous restrictions of avoiding single foods and adding single nutrients to all-encompassing regulation and targeted, individualised comprehensive dietary therapy. The beginning of CSU is not due to a short-term trigger from sensitive foods but rather the result of continuous adverse effects on the immune system caused by prolonged poor diet, such as changes in histamine metabolism and gut microbiota. Otherwise, chronic low-grade inflammation is also a possible cause. The four ways mentioned above can be combined to achieve a safe and effective adjuvant therapy.

4.1. Overall dietary patterns

At present, dietary research at CSU has moved beyond the problem of avoiding single foods to address how to adjust the overall structure of diet and long-term nutritional requirements. In a case-control study, patients with CSU had higher body mass index (BMI) and egg consumption rates than healthy controls, whereas healthy controls had relatively higher caffeine intake. All of the above are reasons for CSU. This study has shown that a poor diet is also one of the reasons for CSU, and therefore, management of diet should be all-encompassing rather than focusing solely on avoiding certain foods.

Based on previous studies and recommendations, the diet of CSU patients should aim to be "anti-inflammatory, gut-protective, nutritionally balanced and immunologically stable". Adopting a low-fat, low-sugar, high-fibre and lightly processed food plan for a long time can increase the number of beneficial bacteria in the gut, maintain the balance of gut microbiota, and reduce intestinal permeability.

At the same time, patients should avoid artificial colours and other chemical additives. They need to eat three regular meals a day, avoid overeating and late-night eating, quit smoking, drinking alcohol, strong coffee and strong tea, maintain intestinal stability and DAO activity, and thus reduce the risk of illness [1, 9]. For example, the Mediterranean diet is rich in polyphenols and unsaturated fatty acids, high in fibre, low in processing, and thus is highly suitable for CSU.

An all-round diet will help to prevent malnutrition and anxiety in the patients, improve their general health, reduce the frequency of relapse, and make it easier for them to live with the treatment over a long period of time compared to the previous single-diet method. However, at present, there are no large-scale clinical trials to support this method, and the evidence is only inferences about the pathogenesis of CSU and indirect evidence from related diseases such as atopic dermatitis [1, 9, 11].

4.2. Individualised nutritional management based on evidence-based grading

Different CSU patients have various causes for their illnesses, different health statuses of the intestines, and different nutritional levels. A uniform diet plan may not be suitable for all people. According to all the evidence-based research results on diet, individualised food plans will be developed for the sick. Podder and others systematically graded the evidence for the CSU dietary strategy to provide an individualised nutrition plan [2] (Table 1). The formulation of individualized nutrition plans should take full account of patients' specific allergens, gut microbiota characteristics, and metabolic markers. In addition, dietary strategies should be regularly modified according to clinical responses during treatment to achieve optimal control.

Table 1. Evidence-based grading and recommended protocols for dietary intervention strategies in CSU

Intervention Protocol	Evidence Strength	Target Population	Usage Principles	Level
Additive avoidance, individualized nutrition, vitamin D supplementation, DAO supplementation, probiotics	High-quality RCT support	All CSU patients	Prioritize and implement long-term routinely as a foundational adjunctive measure	Grade A (Sufficient evidence)
Short-term low-histamine diet, restriction of fish, shrimp, and red meat	Efficacy varies individually	Histamine-intolerant patients	Only for short-term trial; resume dietary diversity after symptom relief	Grade B (Limited evidence)
Gluten-free diet	Only case reports and comorbidity evidence	CSU patients with celiac disease	Not recommended for patients without gluten allergy	Grade C (Conditional)

In combination with the grading strategy, the steps in the clinical standardised individualised diet management process are as follows:

- At various times, measure the serum vitamin D levels for all CSU patients. If the level is low, it should be continued to take vitamin D supplements of 800-2000 IU per day for 8-12 weeks until the serum vitamin D level returns to the normal range [5, 6].
- All CSU patients need to keep a food diary every day and note any symptoms that occur in the two hours after eating. Assess Bowel Function and Tolerance to Trigger Foods.
- All CSU patients should maintain a low-fat, low-sugar, high-fibre and minimally processed diet consistently in the long run. They need to lose weight and change their diet and living habits [1, 9].
- Based on the results of the initial examination, patients with impaired intestinal function can be recommended to use probiotics, patients whose symptoms worsen after consuming high-histamine foods should take DAO supplements, and patients sensitive to "provoking foods" need to avoid eating such food.
- Periodically observe the above indicators to avoid extended, undirected fasting.

5. Conclusion

CSU has a multi-faceted cause. Generally, a second-generation non-sedating H1 antihistamine or the more expensive omalizumab biological agent is used. However, the general response rate of the drugs is not high. Dietary nutritional methods are relatively simple to implement and economically feasible. They can reduce the severity of the disease by regulating histamine metabolism, modifying the intestinal microecology, and adjusting the immune system of the body. In addition, the research direction in clinical medicine has moved from "identifying allergenic foods" to "the immunomodulatory effects of overall dietary patterns". Systematically review the mechanisms of action and clinical evidence for mainstream dietary adjunctive therapies in CSU in this paper.

From the perspective of the mechanism of action, the start of CSU mainly occurs in the following three ways: firstly, an imbalance in histamine. Secondly, disruption of the intestinal microecology. And thirdly, a disturbance in immune regulation. Based on the pathogenesis mentioned above, the three directions for dietary intervention can also be identified: to correct histamine metabolic disorders, a short-term low-histamine diet and avoidance of pseudo-allergens can be implemented to reduce the intake of exogenous histamine. To address dysbiosis in the gut microbiome, probiotics can be used to modulate the composition of gut bacteria and strengthen the intestinal barrier function. And to regulate an aberrant immune response, vitamin D supplementation and the elimination of "trigger foods" may be considered. The general dietary intervention method should focus on "anti-inflammation, intestinal protection and balanced nutrition", and work in conjunction with drug therapy to form a combined treatment system of CSU.

As of now, there is still a lack of large-scale, long-term, high-quality randomised controlled trials to support dietary interventions such as low-histamine diets, pseudo-allergen diets, and "trigger food" diets. Future randomised controlled trials are needed to verify these methods. At present, the only studies on "Fawu" in traditional Chinese medicine have been conducted on animals. Whether the results can be used for patients with CSU still needs to be confirmed in human trials. In addition, the direct causal relationships among the indicators of intestinal flora, DAO activity and intestinal mucosal permeability and the occurrence of CSU have not been fully elucidated. Further research is to be conducted in the future.

In short, dietary nutrition for people with CSU is no longer regarded as an add-on but rather as a new way of personalised, whole-body immune regulation through diet. In the future, in line with clinical medicine, AI and various app systems will be integrated to develop personalised dietary and nutritional intervention plans for individual CSU patients.

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