

# The role of diet in chronic urticaria

Siti Efrida Fiqnasyani, Suci Widhiati, Harijono Kariosentono, Muhammad Eko Irawanto, Triasari Oktavriana

Department of Dermatology and Venereology, Dr. Moewardi General Hospital, Faculty Medicine, Sebelas Maret University, Indonesia 57126.

## Abstract

**Background** Chronic urticaria symptoms are benign and self-limiting. However, chronic urticaria with systemic symptoms can be life-threatening and may be an early sign of anaphylactic shock. This systematic review was conducted to recognize and understand the clinical features of urticaria and the role of diet modification in chronic urticaria to minimise the side effect of long-term therapy.

**Methods** A primary literature search using preferred reporting items for systematic reviews and meta-analyses (PRISMA) was conducted using PubMed and Science Direct databases in January 2021.

**Results** A total of 10 articles were included in this study. Some diets and conditions were recommended to be avoided in patients with chronic urticaria are galactose- $\alpha$ -1,3-galactose allergy ( $\alpha$ -gal), Anisakis simplex, pseudo allergens, gluten, food additives and histamine. Supplementation with diamine oxidase, vitamin D and probiotics was beneficial.

**Conclusion** Diet modification in chronic urticaria patients receiving long-term medical therapy must be done to reduce drug side effects. Consumption of foods suspected of causing urticaria should be avoided for three consecutive weeks, especially for pseudoallergenic foods and histamine-containing foods. Moreover, patients should avoid consuming certain foods that can cause nutritional deficiencies, so further consultation with a nutritionist is needed.

## Key words

Chronic urticaria, hives, dietary, histamine, microbiota.

## Introduction

Urticaria is a common dermatological condition characterised by localised itching, pink plaques or papules measuring several millimetres to centimetres and causing itching.<sup>1</sup> In general, the symptoms of urticaria are benign and self-limiting disease, but urticaria can be an early symptom of anaphylactic shock.<sup>2</sup> Urticaria occurs when immunoglobulin E (IgE) and non-

immunoglobulin E (non-IgE) cause the release of histamine and inflammatory mediators such as mast cells or basophils.<sup>3</sup> Urticaria is divided into acute and chronic. Acute urticaria recurs in less than 6 weeks, whereas chronic urticaria lasts longer, i.e. more than six weeks.

The incidence of chronic urticaria can occur at any age, with a case prevalence of 20% of all skin diseases in the United States in 2019, and most cases (80-90%) are idiopathic chronic urticaria. The prevalence of chronic urticaria was 2256.5 per 100,000 people, and the prevalence increased every year from 2010-2014.<sup>4,5</sup> Rafikasari *et al.* reported that there were 463 new urticaria patients where the majority of

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## Address for correspondence

Dr. Suci Widhiati  
RSUD Dr. Moewardi, Jl. Kolonel Sutarto  
No.132, Jebres, Surakarta, Jawa Tengah,  
Indonesia 57126.  
Ph: (+62)82223363338  
Email: suciwidhiati@staff.uns.ac.id

patients suffering from chronic urticaria due to atopy in Dr. Soetomo Hospital, Surabaya during 2015-2017.<sup>6</sup>

The clinical manifestations of urticaria on the skin surface can be pale to reddish (erythema), round, polymorphic or serpiginous and can quickly appear on other skin surfaces. The onset of urticaria symptoms is relatively rapid, usually occurring within minutes. Chronic urticaria manifests as urticarial lesions lasting more than six weeks.<sup>1,3,6</sup> Chronic urticaria is associated with various clinical presentations characterised by the rapid appearance of oedema (wheal) and angioedema. Wheal has three characteristics: (i) central swelling of varying size; (ii) accompanying itching or sometimes burning; and (iii) short duration, usually 1–24 hours. In 40-50% of cases, urticaria is associated with the appearance of angioedema.<sup>7</sup> Investigations such as complete blood count, erythrocyte sedimentation rate and C-reactive protein can be performed to determine the cause of urticaria.<sup>1,3,6</sup>

Patients with chronic urticaria are advised to make dietary modifications to minimise long-term pharmacological therapy.<sup>5</sup> Several studies have shown that specific dietary changes can improve the prognosis of patients with chronic urticaria.<sup>8–10</sup> The food content that causes chronic urticaria is galactose- $\alpha$ -1.3-galactose ( $\alpha$ -gal) in meat, Anisakis simplex in raw fish, compounds in tomatoes, food additives, cooking spices (herbs), wine and foods with high histamine content.<sup>9</sup> Patients with vitamin D deficiency have a higher risk of developing chronic urticaria. It is necessary to take a patient's history regarding dietary history to identify specific allergens or certain foods that have been consumed, so patients are required to avoid these allergens.

## **Method**

The literature search used the preferred reporting

items for systematic reviews and meta-analyses (PRISMA) guidelines through the PubMed and ScienceDirect databases in January 2021. The terminology used included: “chronic urticaria”, “spontaneous urticaria”, “diet and chronic urticaria”, “food intolerance and spontaneous urticaria”, “dietary modification as skin treatment”, “microbiota”, “milk” and “milk product”. Journals found in the database were then screened based on inclusion and exclusion criteria. The inclusion criteria for articles in the form of clinical studies or research articles that discuss the clinical manifestations of chronic urticaria and the role of diet in chronic urticaria have been published in the last 5 years (2016-2021). Meanwhile, those included in the exclusion criteria are urticaria due to food-intolerance, the role of diet in disorders and other skin conditions (psoriasis, acne, atopic dermatitis and melanoma), the type of study in the form of a review, meta-analysis and case report and the language used in the article is not English or Indonesian.

## **Results**

The primary literature search identified 232 articles from the PubMed database and 717 articles from the ScienceDirect database for 949 articles. The screening was done based on the year of publication, duplication, title and abstract obtained from as many as 36 articles. After being selected using inclusion and exclusion criteria by reading the full paper, it was found that two articles were inaccessible and two articles did not use English/Indonesian, so 10 articles were obtained for analysis. All analysed articles were published in 2016-2021 with a clinical study design.

All selected studies discussed the role or influence of diet on the clinical course of chronic urticaria. We found one article that discussed the effects of food challenge tests, 2

articles discussed the therapeutic effects of a free or low histamine diet, 1 article discussed the effect of a histamine-free low pseudoallergen diet, 1 article discussed the effects of diamine oxidase (DAO) supplementation, 1 article discussed the effects the Mediterranean diet, 1 article discussed the effects of vitamin D, 2 articles discussed gut microbiota dysbiosis in chronic urticaria and 1 article discussed the effects of probiotics. No articles on the effect of milk or dairy products on chronic urticaria met the inclusion criteria. A total of 3 articles used a cohort study design, 4 used a case-control design, and 3 used a randomised-controlled design.

Of the ten articles, 4 of them examined comparisons in 2 groups, namely the group of patients with chronic urticaria and the healthy control group.<sup>3,11-13</sup> The other six studies only examined chronic urticaria patients with details: 4 studies divided subjects into a treatment group and a placebo,<sup>13-16</sup> and 2 studies examined only 1 group, namely patients with chronic urticaria.<sup>2,14</sup>

The average patient subjects involved in the study were adult patients aged 17 years, and only 1 article involved pediatric patients aged 6-12 years, as many as 213 children.<sup>17</sup> Most of the subjects were female, with 1 study having the same comparison between male and female subjects.<sup>2</sup> A total of 6 studies were conducted in Asia,<sup>2,12,13,16,17</sup> and 4 others were conducted outside Asia, such as in Germany, Colombia, and Italy.<sup>3,11,16,17</sup>

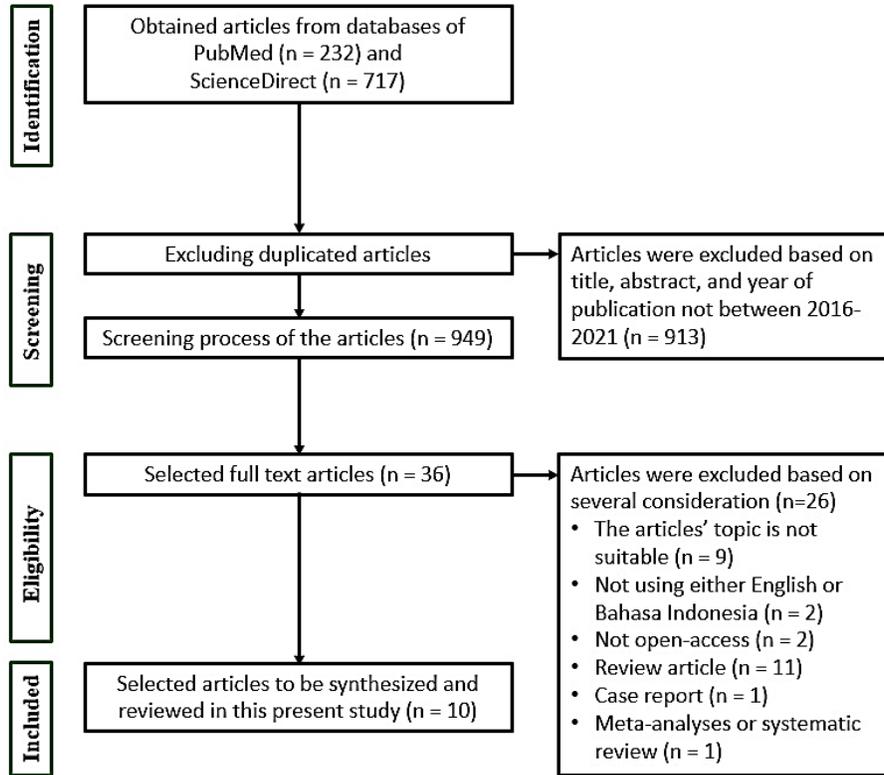
Each study subject was a patient diagnosed with chronic urticaria based on the findings of urticaria/wheal with or without angioedema that persisted for more than six weeks. Patients will be excluded if they have other comorbid diseases that may affect the study, such as systemic or dermatological diseases other than

chronic urticaria. There is 1 study involving subjects with chronic urticaria patients with gastrointestinal symptoms such as meteorism and diarrhoea.<sup>18</sup> Each study provides a different dietary treatment with the duration of the study generally 3-4 weeks<sup>2,14,15,17,18</sup> and carried out for a maximum of 12 weeks in research on vitamin D supplementation. Evaluation of research results was seen based on the UAS-7 score, severity of chronic urticaria, UCT score, DAO activity, plasma histamine levels, quality of life scores (DLQI and CuQ(2)oL) and levels of inflammatory cytokines (TGF- $\beta$ , IL-17, IL-6).

## Discussion

**Urticaria** is a lesion that quickly appears as an erythematous swelling on the skin's surface of the skin's epidermis with various sizes and shapes, itchy with a burning sensation. Due to inflammatory reactions, urticaria lesions do not last long and usually return to normal within 24 hours. Chemokines are the main mediators of causing urticaria.<sup>9</sup> Urticaria is common in all ages, races, genders, occupations, geographic locations and climates.<sup>19</sup> Urticaria episodes lasting more than 6 weeks are usually chronic and are divided into 2 major groups: autoimmune chronic urticaria (45%) and chronic idiopathic urticaria (55%). Research by Siebenhaar *et al.* in 2016 in Germany with a sample of 200 adults aged 20-45 years stated that 13.9% of subjects experienced urticaria. The study reported that 16.5% of the sample had chronic urticaria in less than 12 months, and 22.6% had chronic urticaria throughout their lives. The results of this study indicate a possible higher prevalence of chronic urticaria in the general population.<sup>14</sup>

The most common causes of urticaria are allergens, food pseudo allergens (foods containing histamine or salicylates or others that can produce histamine directly), insect bites, drugs and infections.<sup>3,20</sup>



**Figure 1** The preferred reporting items for systematic reviews and meta-analyses (PRISMA) of this present study.

Physical stimuli such as pressure on the skin, cold air, heat and increased body temperature can cause cholinergic urticaria. Repeated and persistent stimuli cause chronic urticaria in some patients.<sup>3</sup> A history of the disease needs to be done to establish a diagnosis and education about the causative factors that cause urticaria. The clinical findings of urticaria vary widely and depend on the cause.<sup>21,22</sup> Urticaria skin lesions are localised lesions, itching, and superficial oedema limited to the dermis (wheals), which are generally reddish in colour but can turn pale when oedema occurs. Urticarial lesions appear quickly and suddenly after allergen exposure. Lesions rarely persist for more than 24-36 hours and may recur. Urticaria has several subtypes, such as acute or chronic spontaneous urticaria. Spontaneous urticaria lesions may be purpura in more severe cases and persist for several days.<sup>5</sup>

**The dietary role** Diet patterns are very influential on general health. Dietary

recommendations are urgently needed by patients, especially with chronic skin problems and long-term treatment, such as the use of steroids which have various side effects, including affecting metabolic processes, appetite and weight gain.<sup>23-25</sup>

Chronic urticaria often has recurrent episodes of more than 6 weeks. As many as 70-95% of patients with chronic urticaria are idiopathic.<sup>26</sup> Administration of antihistamines as the primary therapy in some cases of chronic urticaria may not be able to control the symptoms that arise, therefore, patients should consider dietary modifications and identify foods that cause urticaria. Foods that potentially cause chronic urticaria include immunological causes (galactose- $\alpha$ -1.3-galactose in meat and Anisakis simplex in fish) and non-immunological (tomatoes, food additives, herbs, wine and foods high in histamine).

**Table 1.** Research characteristics related to the role of diet in chronic urticaria based on the PRISMA.

References	Study design (Location)	Study participants		Results
		Cases	Control	
Sanchez <i>et al.</i> , 2018. <sup>3</sup>	Case-control (Colombia)	164 chronic urticaria patient	38 people (>12 years old without chronic urticaria within 2 years)	The research was conducted using the food challenge tests method (using 410 types of food) in each group of research subjects. Positive results were obtained on the challenge test of 1.2% in the group of chronic urticaria patients (CSU) and 0.7% in the control subjects.
Son <i>et al.</i> , 2018. <sup>2</sup>	Cohort (Kangnam Sacred Heart University Hallym Hospital, South Korea)	22 adult patients (≥18 years old) with chronic urticaria	None	22 adult patients with chronic urticaria were treated with a histamine-free diet for 4 weeks. The severity of urticaria was assessed by the urticaria severity score (USS) and the urticaria activity score (UAS). Plasma histamine levels and diamine oxidase (DAO) activity then Figure 1. The PRISMA6 algorithm was compared before and after the diet. The results of USS and UAS were significantly different before and after a histamine-free diet (p=0.010, p=0.006). There was a significant decrease in plasma histamine levels after diet (p=0.010). There was no significant change in DAO activity (p=0.165).
Wagner <i>et al.</i> , 2016. <sup>18</sup>	Cohort (Germany)	66 chronic urticaria with gastrointestinal involvement (meteorism or diarrhoea)	None	66 chronic urticaria patients with gastrointestinal symptoms were treated with a low histamine diet for at least 3 weeks. UAS was assessed daily, quality of life was assessed using DLQI and CuQ(2)oL questionnaires, and DAO activity was calculated before and after diet therapy. 56 eligible patients entered the study. It was found that 75% of patients experienced improvement after a low histamine diet. 34 of 56 patients (61%) reached the primary study endpoint, with an increase in UAS of 4 from 3. Overall, a significant reduction was achieved from 9.05 to 4.23 points (p=0.004); the mean reduction in the strongly affected subgroup was 8.59 points (p<0.001). DAO activity remains stable. A low histamine diet is a valuable therapy to reduce symptoms and improve the quality of life in chronic urticaria patients with gastrointestinal symptoms.
Siebenhaar <i>et al.</i> , 2016. <sup>14</sup>	Cohort retrospective (Germany)	157 moderate-to-severe degree of chronic spontaneous urticaria	None	157 moderate-to-severe CSU patients (UAS7 10) underwent a histamine-free low pseudoallergen diet for 3 weeks followed by a double-blind placebo-controlled oral histamine provocation (75 mg). A total of 53 patients (34%) had a positive history of histamine intolerance. After the diet, 72 patients (46%) responded with a decrease in CSU activity (a decrease in UAS7 from 7). After a double-blind placebo-controlled trial, 27 patients (17%) gave a positive response. There appears to be little correlation between patient history, response to diet and favourable response to oral histamine

References	Study design (Location)	Study participants		Results
		Cases	Control	
Yacoub <i>et al.</i> , 2018. <sup>15</sup>	A randomised double-blind placebo-controlled study (San Raffaele Research Hospital Milan, Italy)	22 chronic spontaneous urticaria	None	provocation. Patients were given oral DAO supplementation for 30 days (1 capsule 2x daily, 15 minutes before meals), and then the severity of CSU was measured with a UAS-7 score and compared with a placebo. A total of 20 patients completed the study. Adjunctive DAO therapy decreased mean score of $3.8 \pm 1.2$ points $\pm$ SEM UAS-7 in patients with low serum DAO levels at time 0 ( $p = 0.041$ compared with placebo). The degree of increase in UAS-7 was inversely proportional to the basal DAO level ( $p = 0.019$ ). Patients receiving DAO supplementation could slightly reduce the daily dose of antihistamine medication ( $p = 0.049$ ). Data show DAO supplementation can effectively relieve urticaria symptoms in patients with low serum DAO levels.
Ayvaz and Kuyumcu, 2021. <sup>11</sup>	Cross-sectional and case-control (Dermatology Hospital of Suleyman Demirel University, Turkiye)	100 chronic spontaneous urticaria	100 healthy people	Subjects were given a Mediterranean diet, then evaluated with a diet score questionnaire, and assessed the UAS score for 7 days and UCT. The results showed that the patient group's average Mediterranean diet score was $5.40 \pm 1.88$ , while in healthy controls, it was $6.30 \pm 1.39$ ( $p < 0.001$ ). The patient's UAS7 score was negatively correlated with the Mediterranean diet score, whereas the UCT score was positively correlated. Adherence to the Mediterranean diet can reduce the risk and severity of symptoms of chronic spontaneous urticaria.
Mony <i>et al.</i> , 2020. <sup>16</sup>	Randomised controlled trial (Tertiary JIPMER Hospital, India)	120 chronic spontaneous urticaria with vitamin-D deficiency	None	UAS-7 scores and autologous plasma skin test (APST) status were assessed in all patients. CU patients were given vitamin D supplementation at a dose of 60,000 IU every two weeks for 12 weeks, and those in the placebo group received an appropriate placebo. 5 mL of blood was drawn from all study subjects at baseline and after 12 weeks. There was a significant decrease in UAS7 scores and inflammatory cytokines after 12 weeks in the vitamin D group compared with the placebo. Vitamin D supplementation in chronic urticaria patients with vitamin D deficiency has been shown to significantly reduce disease severity, which may be mediated through the reduction of systemic inflammation.
Zhang <i>et al.</i> , 2021. <sup>12</sup>	Case-control (University of Xi'an Jiaotong Hospital)	20 chronic spontaneous urticaria	20 healthy people with sex and age adjustment	This study was to identify potential genetic composition and function in faecal microbiota between patient and control groups. Intestinal microbiota of CSU patients and healthy individuals were obtained by massive 16s rRNA sequencing. The results showed that Firmicutes, Bacteroidetes, Proteobacteria and Verrucomicrobia were the dominant microbiota in CSU. Differential analysis showed that the relative abundance of Proteobacteria ( $p = 0.03$ ), Bacillus ( $p =$

References	Study design (Location)	Study participants		Results
		Cases	Control	
				0.04), Enterobacterales (p = 0.03), Enterobacteriaceae (p = 0.03) was significantly increased in CSU patients. In contrast, in CSU patients, the Megamonas, Megasphaera and Dialister (all p < 0.05) significantly decreased compared to the control group. Different microbiological compositions affect normal GIT function. CSU patients exhibited gut microbiota dysbiosis compared to healthy controls.
Rezazadeh <i>et al.</i> , 2018. <sup>13</sup>	Case-control (Urmia, Iran)	20 chronic urticaria	20 healthy people with sex and age adjustment	This study was to identify potential genetic composition and function in faecal microbiota between patient and control groups. Intestinal microbiota of CSU patients and healthy individuals were obtained by massive 16s rRNA sequencing. The results showed that Firmicutes, Bacteroidetes, Proteobacteria and Verrucomicrobia were the dominant microbiota in CSU. Differential analysis showed that the relative abundance of Proteobacteria (p = 0.03), Bacillus (p = 0.04), Enterobacterales (p = 0.03), Enterobacteriaceae (p = 0.03) was significantly increased in CSU patients. In contrast, in CSU patients, the Megamonas, Megasphaera and Dialister (all p < 0.05) significantly decreased compared to the control group. Different microbiological compositions affect normal GIT function. CSU patients exhibited gut microbiota dysbiosis compared to healthy controls.
Bi <i>et al.</i> , 2021. <sup>17</sup>	Randomised placebo-controlled study (Henan, China)	213 pediatric patients aged 6-12 years with chronic urticaria (108 = received Yimingjia probiotic therapy, 105 = placebo)	None	Children in each group were treated with desloratadine dry suspension, and those in the treatment group also received Yimingjia. Efficacy was evaluated at weeks 1, 2 and 4. The study obtained 206 eligible subjects with 104 treatment groups and 102 placebo groups. The results showed that clinical symptom scores were not significantly different at weeks 1 and 2 (p > 0.05), but at week 4, the size of urticaria and the frequency of attacks were significantly reduced in the treatment group (p = 0.049 and 0.03). The overall response rate differed significantly between the treatment (80.8%) and placebo (62.5%) groups ( $\chi^2 = 4.20$ , p = 0.04).

Various studies have shown diet's role in improving the clinical condition of urticaria. A case-control observational study by Ayvaz and Kuyumcu in 2021 proved that adherence to the Mediterranean diet (a healthy diet of vegetables, fruit, seafood and a restrictive pseudoallergenic diet) was an independent factor that could reduce the incidence and severity of symptoms of chronic spontaneous urticaria. Adoption of a healthy lifestyle and diet is essential and should be combined with holistic management of patients with chronic spontaneous urticaria.<sup>11</sup>

The effectiveness of a low histamine diet needs further research because there are still few patients who apply a low histamine diet or a low histamine diet as well as a pseudo allergens free diet. There is no supporting data to assess the safety of low histamine and pseudoallergen-free diets. The long-term consequence of a low histamine diet is an increased risk of malnutrition, but there are no definitive data to support the safety and effectiveness of dieting in chronic urticaria.<sup>27</sup>

Food allergy due to immunological mechanisms is a rare cause of chronic urticaria. Sanchez *et al.* in 2018 conducted a study using the food challenge tests method (using 410 types of food) on 164 patients with chronic urticaria and 38 controls. Patients taking antihistamines daily should stop temporarily for at least four days before the food challenge tests are performed. Positive results with the appearance of urticaria or angioedema on the challenge test were 1.2% in chronic urticaria patients and 0.7% in control subjects.<sup>3</sup>

Several foods consumed are reported to worsen symptoms of chronic urticaria, including alcohol, food additives, seafood, some fruits and vegetables, and fermented foods. Diagnosis and therapy for urticaria can be by changing the type of food that causes urticaria, oral provocation

testing (OPT) or avoiding foods that cause urticaria.<sup>28,29</sup>

**Galactose- $\alpha$ -1.3-Galactose** Galactose- $\alpha$ -1.3-galactose ( $\alpha$ -gal) is an oligosaccharide expressed in mammalian glycoproteins and glycolipids. Patients with  $\alpha$ -gal-specific IgE will experience hypersensitivity to red meat. Production of  $\alpha$ -gal-specific IgE occurs as a result of tick bites. Consumption of red meat containing  $\alpha$ -gal will cause specific IgE activation and will cause clinical manifestations of urticaria. In a 2019 study by Wilson *et al.* in 245 patients, 93% had urticaria, 64% had gastrointestinal disturbances, and 60% had anaphylactic symptoms.<sup>30</sup> The onset of symptoms due to  $\alpha$ -gal hypersensitivity usually occurs later, i.e. 2-6 hours after meat consumption. Wilson *et al.* found that in patients with chronic urticaria, it was found that 20 of 29 patients had serum  $\alpha$ -gal antibodies, and fleas had bitten 95% of them as transmission animals. The study also stated that avoiding meat consumption led to total remission of chronic urticaria in 9 patients and partial remission in 5 patients.<sup>30</sup>

**Anisakis simplex** (*A. simplex*) is a parasitic nematode from the Anisakidae family that is often found as a parasite on various seafood such as fish, squid and marine mammals. Hypersensitivity to *A. simplex* can cause chronic urticaria due to the consumption of undercooked fish. A 2013 randomised controlled trial by Ventura *et al.* in 213 subjects with chronic urticaria showed 50% allergic reactions when sensitised to *A.*<sup>31</sup> *simplex* based on skin prick test results. Improvements in chronic urticaria were also obtained by avoiding the intake of foods containing fish-based ingredients, especially those not entirely cooked within six months in 77% of subjects and 2% of controls.

Mast cell activation in patients with chronic urticaria and parasitic infections such as *A.*

simplex can cause specific proinflammatory mediators such as IgE, T-helper2 (Th2) cytokines, recruitment of eosinophils near the skin epidermis and activation of coagulation factors and the complement system. Recent research explains that patients who are allergic to A simplex can consume other processed fish that is frozen (-20°C for 48 hours). Grilled fish is not recommended because A. simplex remains stable during the roasting process.<sup>29</sup>

**Gluten** is a protein found in grains, cereals, wheat, rye, and barley. Celiac disease is an autoimmune disease associated with chronic urticaria. Celiac disease is an intestinal mucosal disorder that causes gluten malabsorption. The pathophysiology of the appearance of skin manifestations in celiac disease is still not well understood. In a recent research study, patients with celiac disease experienced chronic urticaria due to the consumption of foods containing gluten.<sup>26</sup>

**Pseudoallergen** Reactions due to pseudo allergens are hypersensitivity because they do not involve the allergen and do not occur purely due to allergies. The mechanism of action is not known with certainty. There is no IgE increase, and the skin prick tests on the skin results are negative. Various types of food and beverages can become pseudo allergens, including natural food ingredients, such as fruits, vegetables, food additives (added colourants, preservatives, flavourings) and vasoactive compounds (acetylsalicylic acid, histamine and sodium oxide).<sup>3,29</sup>

**Histamine** Histamine is a vasoactive amine released from mast cells and is an important mediator of chronic urticaria. Antihistamines are the mainstay of therapy. Foodstuffs with high microbial activity have higher histamine content. Intolerance to histamine can occur even if only consuming foods that contain low levels of

histamine.<sup>32</sup> Studies have shown that a low-histamine diet is adjuvant therapy for chronic urticaria.<sup>18,33</sup>

Patients with chronic urticaria reported improvement with a low-histamine diet. This is because on a diet high in histamine, the enzyme diamine oxidase (DAO) levels will decrease. Diamine oxidase is an enzyme that plays a role in preventing the entry of histamine from the diet into the bloodstream. An increase in circulating histamine levels will cause clinical manifestations of urticaria.<sup>34</sup> A study by Yacoub *et al.* in 2018 studied 22 patients with chronic spontaneous urticaria who were given 30 days of oral DAO supplementation (1 capsule 2x daily, 15 minutes before meals). Patients were then measured for the severity of urticaria with a UAS-7 score and compared with a placebo. The results showed that additional DAO therapy decreased UAS-7 scores in patients with low serum DAO levels at time 0. The data show that DAO supplementation can effectively relieve urticaria symptoms in patients with low serum DAO levels.<sup>15</sup>

A study by Straesser *et al.* in the United States conducted on 157 subjects who consumed a histamine-free, low-pseudoallergen diet, 46% reported improvement. Oral histamine administration trials can produce a 50% response, even in patients with no history of food intolerance.<sup>35</sup> A 2016 study by Siebenhaar showed that histamine intolerance is a relevant cause in a minority of patients with chronic spontaneous urticaria. Symptoms of 46% of the chronic spontaneous urticaria patients included in this study improved significantly after a low histamine and pseudo allergen diet, consistent with response rates of 73% and 28% of previous reports, respectively. Less than half of the 60 patients with chronic spontaneous urticaria with histamine intolerance confirmed by provocation testing show an urticaria response, and less than

10% of these patients have problems with histamine-rich foods and get better after avoiding the histamine diet.<sup>23</sup>

A study showed that the effects of a histamine-free diet were evaluated in 22 patients with chronic spontaneous urticaria, in whom there was a significant reduction in disease severity and plasma histamine levels and the severity of symptoms of chronic spontaneous urticaria.<sup>2</sup> A low histamine diet is a beneficial, simple and cost-effective therapy to reduce symptoms and improve the quality of life of patients with chronic spontaneous urticaria who have gastrointestinal symptoms.<sup>18</sup>

**Vitamin D** also known as calciferol, is a fat-soluble vitamin naturally found in several foods such as seafood, fish oil, salmon, tuna, milk and dairy products, mushrooms, liver, and egg yolks. Vitamin D can also be an additive in other foods and is often found as a dietary supplement.<sup>36,37</sup> Vitamin D supplementation may improve symptoms of chronic urticaria, especially in patients resistant to standard therapy.<sup>39</sup> Chronic urticaria is known to be closely associated with autoimmunity. Vitamin D plays a vital role in the regulation of the innate and adaptive immune systems, so vitamin D supplementation is beneficial for patients with chronic urticaria.<sup>38</sup>

Mony *et al.* conducted a study of 120 patients with chronic urticaria with vitamin D deficiency. Patients were given vitamin D supplementation at a dose of 60,000 IU every two weeks for 12 weeks, and those in the placebo group received an appropriate placebo. There was a significant reduction in UAS-7 scores and inflammatory cytokines after 12 weeks in the vitamin D group compared with placebo.<sup>15</sup> Vitamin D supplementation in chronic urticaria patients with vitamin D deficiency demonstrated a significant reduction in disease severity which may be mediated through the reduction of

systemic inflammation.<sup>16</sup>

**Gut microbiota and probiotics** The regulation of the immune system is one of the important roles of the gut microbiota. Several studies have shown the role of microbiota in allergic diseases such as asthma, food allergies and atopic dermatitis.<sup>39</sup> Decreased exposure to the immunomodulatory effects of the gut microbiota leads to an increased incidence and prevalence of allergies as well as autoimmune and inflammatory disorders.<sup>40</sup>

Research by Rezazadeh *et al.* in 2018 by comparing the frequency and number of Lactobacillus, Bifidobacterium and Bacteroides bacteria between patients with chronic urticaria and healthy controls showed that all stool samples were positive for Lactobacillus and Bifidobacterium; however, Bacteroides was not detected in the faecal samples of the control and patient groups (5% and 15%, respectively). The results showed no significant difference between the frequency of Lactobacillus, Bifidobacterium and Bacteroides in stool samples from healthy controls and chronic urticaria patients. Based on qPCR, the mean folds of Lactobacillus and Bifidobacterium in faecal samples of the control group were significantly higher than that of patients with chronic urticaria; however, the difference in mean Bacteroides folds was not statistically significant.<sup>13</sup>

The potential protective effect of Bifidobacterium and Lactobacillus in chronic urticaria may be due to several mechanisms, such as the induction of regulatory T cells (Treg) by these bacteria. Treg cells can reduce inflammation through the secretion of anti-inflammatory mediators and an anti-inflammatory environment protective against chronic urticaria. Improvement of the composition of the gut microbiota is a possible mechanism that can be suggested to exert the

protective effect of these bacteria against chronic urticaria.<sup>13</sup>

Zhang *et al.* in 2021 compared the gut microbiota of a group of patients with chronic spontaneous urticaria with a control group and found significant differences in the relative abundance of flora in patients with chronic spontaneous urticaria, especially Proteobacteria, Bacillus and Enterobacteriales, which are abnormal in other diseases. This study demonstrated gut microbiota dysbiosis in chronic spontaneous urticaria and suggested that the gut microbiota may influence the pathogenesis of chronic spontaneous urticaria through metabolic abnormalities.<sup>12</sup>

Probiotic bacteria are commonly found in the breakdown of dairy products and secrete lactic acid through carbohydrate fermentation. Probiotics are “live microorganisms that exert a beneficial effect on the host”. Probiotics can prevent allergic responses due to their anti-inflammatory effects, alter the balance of Th1/Th2 to Th1 by inhibiting Th2 cytokines or indirectly induce the production of IL-10 and Treg cells through the maturation of dendritic cells or toll-like receptors. A study by Bi *et al.* in 2021 examined 16 206 children with chronic urticaria and reported that the scores of clinical symptoms of urticaria between the probiotic group and the placebo group did not differ significantly at weeks 1 and 2. However, at week 4, the size of urticaria and the frequency of attacks were not significantly different reduction in the treatment group.<sup>17</sup> The overall response rate differed significantly between the treatment (80.8%) and placebo (62.5%). The finding of altered gut microbiota in chronic urticaria patients causes intestinal microbiota dysbiosis and may be corrected using probiotic supplementation.

## Conclusion

From a total of 10 articles reviewed, it was found that a low or histamine-free diet followed by a pseudo-allergen-free diet was proven to have a good effect on the clinical symptoms of chronic urticaria to improve the quality of life of patients. Supplementation with DAO and vitamin D also relieves the symptoms and severity of chronic urticaria. In addition, avoiding foods containing galactose- $\alpha$ -1,3-galactose allergy ( $\alpha$ -gal), Anisakis simplex and gluten are also known to improve the clinical course of chronic urticaria. Several studies have shown intestinal microbiota dysbiosis plays a role in the pathogenesis of chronic urticaria through metabolic disorders. One way to correct intestinal microbiota dysbiosis in chronic urticaria is by administering probiotics.

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