



ORIGINAL ARTICLE

A Histamine-Free Diet Is Helpful for Treatment of Adult Patients with Chronic Spontaneous Urticaria

Jee Hee Son*, Bo Young Chung*, Hye One Kim[†], Chun Wook Park[†]

Department of Dermatology, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea

Background: In adult patients with chronic urticaria (CU), the prevalence of food allergy is low compared to childhood patients. However, there are many patients who report food-related aggravation of CU, and some of them may have histamine intolerance. **Objective:** The aim of this study was to evaluate the role of ingested histamine and to investigate the effect of a histamine-free diet in adult patients with CU.

Methods: Twenty-two adult patients with CU were enrolled. Foods with high amounts of histamine were prohibited to all patients for four weeks. The degree of severity of the urticaria was evaluated using the urticaria severity score (USS) and urticaria activity score (UAS). Plasma histamine levels and diamine oxidase (DAO) activity were determined and compared before (baseline) and after the histamine-free diet.

Results: Twenty-two adult patients were recruited and completed four weeks of histamine-free diet. The USS and UAS scores each showed significant differences before and after the histamine-free diet ($p=0.010$, $p=0.006$). There was a sig-

nificant reduction in plasma histamine level after the histamine free-diet, compared with baseline ($p=0.010$). However, DAO activity did not change after the histamine-free diet ($p=0.165$). **Conclusion:** Our study suggested that ingested histamine might be related to CU severity and that a histamine-free diet is helpful for treatment of adult patients with CU. (*Ann Dermatol* 30(2) 164~172, 2018)

-Keywords-

Diet therapy, Food intolerance, Histamine, Urticaria

INTRODUCTION

Urticaria is a common skin condition associated with immunological and non-immunological mechanisms. It can be caused by release of many mediators, such as histamine, from skin mast cells and by an increase in the blood vessel permeability. This leads to temporary leakage and accumulation of plasma in tissues and to cutaneous symptoms, such as itchy wheals or swelling¹. Chronic urticaria (CU) is defined as frequent episodes of urticaria that last more than six weeks². However, most cases (~70% to 95%) of CU patients remain idiopathic³ and treatment options are limited. The mainstay of therapy is symptomatic control with antihistamines⁴. Itching is sometimes not controlled by antihistamines, so physicians may encounter challenges when treating patients with CU^{2,4}.

So-called food allergy, despite negative food allergy test results, is common⁵. As several foods may contain high amounts of histamine, their ingestion may be responsible for some cases of food intolerance, which may include allergic like symptoms such as sneezing, flush, headache, diarrhea, and even shortness of breath^{5,6}. There is an explanation for this phenomenon: disturbances in the metabolism of ingested histamine in patients with CU and in-

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*These authors contributed equally to this work and should be considered co-first authors.

[†]These authors contributed equally to this work and should be considered co-corresponding authors.

Corresponding authors: Chun Wook Park, Department of Dermatology, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, 1 Singil-ro, Yeongdeungpo-gu, Seoul 07441, Korea. Tel: 82-2-829-5221, Fax: 82-2-832-3237, E-mail: dermap@hanmail.net

Hye One Kim, Department of Dermatology, Kangnam Sacred Heart Hospital, Hallym University College of Medicine, 1 Singil-ro, Yeongdeungpo-gu, Seoul 07441, Korea. Tel: 82-2-829-5221, Fax: 82-2-832-3237, E-mail: hyeonekim@gmail.com

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creased mucosal passage of histamine^{6,7}.

Histamine belongs to the biogenic amines, one of the important mediators for urticaria. Histamine intolerance results from disequilibrium between the accumulated histamine and the capacity for histamine degradation. Exceeding the histamine tolerance level of an individual gives rise to concentration-dependent histamine-mediated symptoms such as increasing gastric acid secretion and heart rate (1~2 ng/ml), tachycardia, headache, flush, urticaria, pruritus (3~5 ng/ml), decreased arterial pressure (6~8 ng/ml), bronchospasm (7~12 ng/ml), and cardiac arrest (<100 ng/ml). These can occur when patients take foods rich in histamine or impaired histamine degradation based on reduced diamine oxidase (DAO) activity, the main enzyme catabolizing histamine in the gut^{7,8}. These can be described as histamine-mediated pseudo-allergic reactions or pseudo-food allergies, because the clinical manifestations mimic immunoglobulin (Ig)E-dependent immunologically-mediated allergic diseases without distinct immunologic sensitization⁹. There are many reports that showed lower DAO activity of CU patients compared with healthy controls^{7,10}, even another study does not support this¹¹. *Anisakis* species, roundworm parasites that have lifecycles involving fish and marine mammals, are infective to humans and cause anisakiasis. People who produce IgE in response to this parasite may subsequently have an allergic reaction, including anaphylaxis, after eating fish infected with *Anisakis* species. It was reported that DAO levels in CU depend on fish-eating habits, and in CU with sensitization against *Anisakis*, on the amount of specific IgE production¹¹. Also, it was reported that there were no significant differences in DAO activity among CU patients without gastrointestinal (GI) symptoms, CU patients who frequently experienced GI symptoms, and healthy control subjects¹². Until now, the association between excessive intake of histamine-rich food and symptoms of CU has been controversial. Siebenhaar et al.¹³ reported CU due to histamine intolerance appears to be rare; only a few patients with CU respond to oral histamine provocation. However, there have been many studies about the effectiveness of histamine restriction or histamine-free diet for CU^{5,9,10,13,14}.

In a previous study, we tried to evaluate the effect of a histamine-free diet on CU patients but there was no significant improvement of symptoms or decrease in the number of antihistamine tablets taken in the restricted diet groups, compared with the control group¹⁵. However, there were limitations to the study: that many patients suffered difficulties trying to fulfill the restricted diet strictly and making out a menu by themselves. Also, in Korea, fermented foods, such as kimchi (fermented cabbage or rad-

ish), soybean paste, and red pepper paste, are frequently consumed. However, not many papers report studies on the histamine content in such fermented foods and the restriction of these fermented foods was not done in the previous study.

Therefore, we consulted with the Department of Nutrition and made a standard menu for seven days based on a histamine-free diet. We also evaluated the histamine levels of preferred Korean foods, including fermented foods, and measured changes in the histamine levels in relation to the cooking method. Based on that study¹⁶, the current prospective study was initiated to systematically examine the role of a histamine-free diet for improving the symptoms of CU with regular previous standard treatment.

MATERIALS AND METHODS

Patient selection

We enrolled 22 patients (≥ 18 years of age) with physician-diagnosed CU who visited between September 2014 and December 2015. Two dermatologists in the hospital diagnosed patients according to their symptoms and history. Diagnosis of CU was defined according to the criteria of Warin and Smith (1976)¹⁷ which included whealing and/or angioedema lasting longer than six weeks and occurring at least twice a week. We included the patients who could make and control their menu according to study instructions and whose symptoms were not controlled by standard therapy (steroid, H1 anti-histamine). Patients who had any dermatologic or systemic diseases (atopic dermatitis, diabetes, chronic renal failure, etc.) that could induce itching, and uncontrolled chronic diseases, were excluded. Patients with diseases (inflammatory bowel disease, squamous cell carcinoma, acute epipharyngitis) and drugs (heparin, cimetidine, aminoguanidine, chloroquine, dihydralazine, isoniazid, cefuroxim, cefotiam, chloroquine, aminophylline, verapamil, alprenolol, dihydralazine, contrast media, opiates, etc.) that could affect histamine release and DAO activity, pregnant patients, patients with any abnormalities discovered in physical examination, and patients with food allergy were also excluded. Patients who visited our clinic for the first time were asked to bring their previous prescriptions, and detailed medical records and history taking were used to confirm whether their condition meet the inclusion criteria or not.

All patients were on a free and uncontrolled diet before starting the study. We evaluated plasma histamine level and DAO activity before and after a histamine-free diet. Before entering the study, all patients were evaluated by their history and by the MAST Korean IgE Panel (MAST

Immunosystem, Inc., Mountain View, CA, USA) to exclude food allergy. Informed consent was obtained from all patients and approval for the study was obtained from the university's standing committee on ethical practice (Hallym University Kangnam Sacred Heart Hospital Institution Review Board no. 2014-10-138).

During the period of study, oral antihistamine and topical steroids for CU were allowed. However, to evaluate the effect of histamine-free diet, the amount and kinds of drugs for CU treatment could be reduced from the baseline but could not be increased. For the patients who visited our clinic for the first time, the amount and kinds of drugs for CU treatment were not changed at their first visit to Kangnam Sacred Heart Hospital, Department of Dermatology. Patients were also excluded if the amount or kinds of drugs they used had to be increased.

Methods

1) Histamine-free diet

Patients restricted foods with high histamine levels for four weeks, based on previous studies¹⁶. We educated patients to restrict histamine-rich foods such as tuna, mackerel, Pacific saury (mackerel pike), pork, chicken, and spinach. This included in particular, fermented foods such as fermented cabbage or radish, soy bean paste, red pepper paste, mayonnaise, yogurt, cheese, ketchup, wine, and beer, which have large amounts of histamine. The food ranking by histamine level result from our previous study is summarized in Supplementary Table 1. Along with these, instant foods, grapes, bananas, strawberries, and citrus fruits known to release histamine (lemons, oranges, tangerines), as well as pineapples, tomatoes, nuts including peanuts, alcoholic beverages including wine, green tea, and chocolate were also restricted. The Department of Nutrition supplied a reference menu to patients and consulted with them to preventing nutritional imbalance. An example of the menu is presented in Table 1.

2) Measurement of serum histamine level and diamine oxidase activity

Blood was drawn from each patient during urticaria skin reactions. Plasma was separated and kept at -20°C until needed. Histamine assays were performed using enzyme-linked immunoassay kits (ELISA; IBL International GMBH, Hamburg, Germany). DAO activity was assayed using the ELISA kit (Cusabio Biotech Co., Ltd., Wuhan, China).

3) Severity evaluation of chronic urticaria

To evaluate the severity of CU before and after the his-

tamine-free diet, the urticaria severity score (USS) and urticaria activity score (UAS) were used^{18,19}. All patients were recommended to visit the outpatient clinic every week and to submit their self-reported note of daily UAS. UAS was composed of the number of wheals and the degree of pruritus. The score of each portion ranges from '0' to '3,' so the total scores ranged from '0' to '6.' In this study, we used UAS7. Patients recorded their daily UAS and calculated scores over seven days for total scores of the week (UAS7), and checked for changes every week. This method (UAS7) requires a week to score; so it was hard for us to get the UAS (UAS7) score at the baseline in this study. The UAS7 ranges from 0 to 42. The USS was composed of several questions such as the degree of pruritus that week, days of hives that week, average hours or hives each day, body distribution of hives, daily average, average antihistamine pills daily, average prednisone pills daily, nights of hives and sleep interference, hive interference with work, school or social life, and so on. The USS of each patient was evaluated two times, at the baseline and after four weeks of histamine-free diet. The USS ranges from 0 to 92. All assessment was done by one dermatologist.

Statistical analysis

The Wilcoxon signed rank test for variables, such as serum histamine level, DAO activity, and clinical severity using USS and UAS, were used to determine the significance of differences before and after the histamine-free diet. In all subjects with blood samples, the relationship between DAO activity and plasma histamine concentrations, the relationship between USS or UAS and plasma histamine concentrations, and the relationship between DAO activity and USS or UAS; were evaluated by Pearson, Spearman, or Kendall correlation. Significance levels for all analyses were set at $p < 0.05$. All statistical analysis was performed using PASW Statistics ver. 18.0 for Windows (IBM Co., Armonk, NY, USA).

RESULTS

The baseline patient characteristics

Overall, 22 adult patients with CU were involved in the study and all finished four weeks of the histamine-free diet. Among patients who completed the study, 11 were male and 11 were female. The average of their ages was 41.2 ± 16.1 (range, 18~70 years old). The average of their duration of treatment before enrollment was 22 ± 25.2 (range, 0~73) months.

Table 1. Example of an experimental menu: a histamine-free diet

	Breakfast	Lunch	Dinner
1st day	White rice Bean sprouts soup Bulgogi Soy sauce braised potatoes Seasoned Chamnamul	Rice with sorghum Fish cake soup Grilled yellow croaker Balloon flower root salad Seasoned bean sprouts	White rice Dried pollack soup Grilled tofu Steamed egg Bracken salad
2nd day	White rice Egg soup with chives Steamed tofu Stir-fried shitake Grilled sweet pumpkin salad	Rice with millet Radish soup with mussel Stir-fried mushroom Steamed egg Seasoned pigweed	White rice Radish soup with beef Grilled yellow croaker Black bean boiled in soy sauce Green pumpkin salad
3rd day	Cereal flakes Milk	Rice with pea Potato hand-pulled dough soup Grilled beef Grilled tofu Stir-fried fish cake and vegetables	White rice Soft tofu stew Grilled sole Cucumber salad Soy sauce braised potatoes
4th day	White rice Soft tofu stew Steamed egg Seasoned acorn jelly salad Seasoned water parsley	White rice Tteokguk with beef Grilled pomfret Seasoned aster Stir-fried chopped potato	White rice Hot bean sprouts soup Bulgogi Steamed egg Seasoned pigweed
5th day	White rice Radish soup with perilla Grilled yellow croaker grilled deodeok root Seasoned bean sprouts	White rice Egg soup Grilled tofu Seasoned green pumpkin Seasoned perilla leaf	White rice Codfish soup Grilled beef Grilled tofu Cucumber salad
6th day	Rice with sorghum Beef bone soup Grilled tofu Lettuce wrap Broiled parsley	White rice Bean sprouts soup Bulgogi Cucumber salad Seasoned pepper and lettuce	White rice Fish cake soup Steamed soft soybean curd Radish salad Lotusroot boiled in soy sauce
7th day	Toast Soymilk or milk	White rice Chilled cucumber soup Steamed soft soybean curd Black bean boiled in soy sauce Radish salad	White rice Bean sprouts soup Bulgogi Soy sauce braised potatoes Seasoned Chamnamul

Please use as small amounts of seasonings as possible. Season with salts, vinegar and ground pepper rather than soy sauce, soybean paste and red pepper paste.

Please avoid boiling in soy sauce. Boiling is recommended than grilling.

Menu is exchangeable. For balanced diet, divide foods to rice, main dish and side dishes and menu change should be done within same division (ex. White rice can be exchanged to rice with sorghum or rice with pea, not to bulgogi which is considered as main dish).

Pan-frying and deep-frying is possible (ex. Pan-fried beef meat bal, pumpkin pancake, sweat and sour beef, deep-fried lotus root and deep fried eggplant).

The effect of the histamine-free diet on the clinical severity of chronic urticaria

The baseline USS was 25.023 ± 11.433 (range, 7.5 ~ 15.4). The UAS (UAS7) of the first week was 10.263 ± 9.216 (range, 0 ~ 34). After four weeks of histamine-free diet, USS was 16.227 ± 12.794 (range, 0.5 ~ 42; Fig. 1) and UAS was 4.056 ± 4.143 (range, 2 ~ 21; Fig. 2). The scores of USS and UAS were quite low and reflect that antihist-

amines for these patients were continuously prescribed. These measures were reduced after histamine-free diet and statistically significant ($p=0.010$ and 0.006 , respectively). In the case of UAS, the scores of week 2 and week 3 were reduced to 7.895 ± 9.014 , 7.278 ± 9.134 , respectively. They were all statistically significant ($p=0.004$ and 0.003) (Fig. 2).

The changes of individual urticaria severity score scores and medication use

To delineate the specific symptoms or severity that were potentially driving these differences in total USS score between baseline and after the histamine-free diet, the results of the individual questions on the 12-point USS questionnaire were analyzed (Fig. 3). Interestingly, after the histamine-free diet, there were reports of decreased degree of pruritus in the past week, decreased number of days with hives, decreased body distribution of hives on an average day, and decreased body distribution of hives on the worst day ($p=0.031, 0.034, 0.027,$ and 0.035). There were also decreased interference with work/school

($p=0.005$) and social life ($p=0.026$). There were no differences in the average hours of hives each day or maximum hours with hives each day, although these question items were generally scored low. There were also trends toward decreased number of days with swelling ($p=0.197$) and decreased interference with sleep ($p=0.276$), but these were not statistically significant. In cases of medication, there was no difference in the average number of daily antihistamine pills ($p=0.105$) or prednisone pills ($p=0.785$).

The changes of serum histamine level and diamine oxidase activity

Blood sampling after consent was done for only 19 of the 22 patients. Normally, histamine was not detectable (less

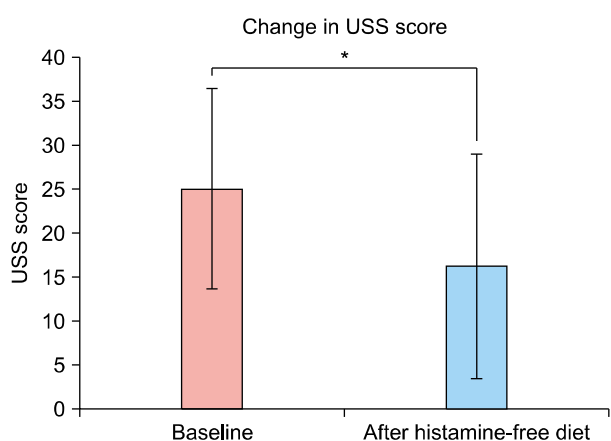


Fig. 1. Change in the urticaria severity score (USS) after four weeks of histamine-free diet. Data are presented as mean and standard error (bars), with statistical significance denoted by lines and asterisks ($p=0.010$). $*p<0.05$.

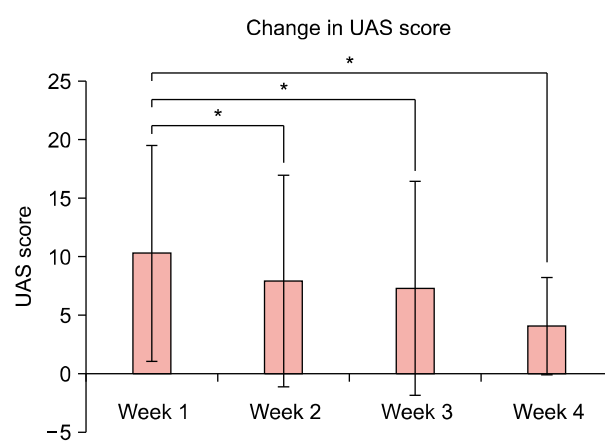


Fig. 2. Change in the urticaria activity score (UAS) with time in histamine-free diet for four weeks. Data are presented as mean and standard error (bars), with statistical significance denoted by lines and asterisks ($p=0.006$). $*p<0.05$.

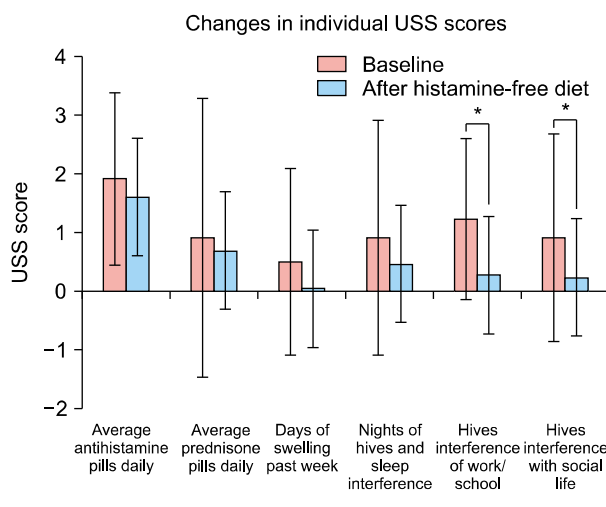
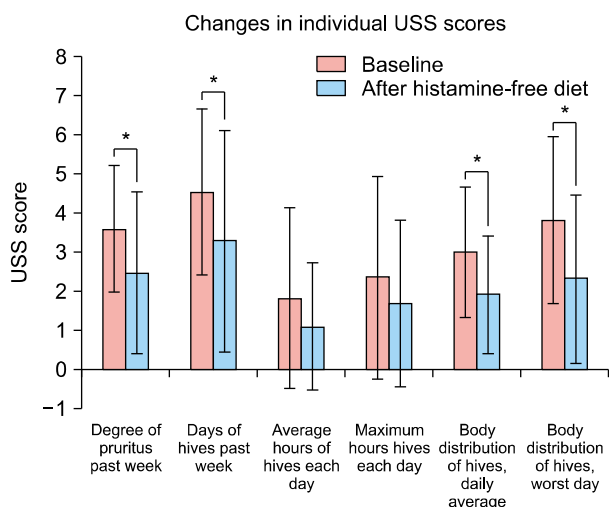


Fig. 3. Changes in the individual urticaria severity score (USS) components before (baseline) and after the 4-week histamine-free diet. Data are presented as mean and standard error (bars), with statistical significance denoted by lines and asterisks. $*p<0.05$.

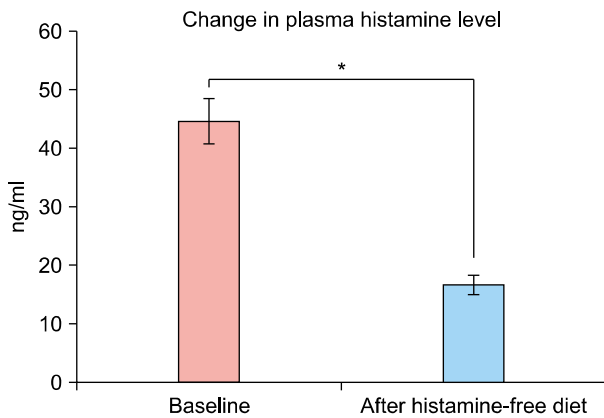


Fig. 4. Change in the plasma histamine level after a 4-week histamine-free diet: Data are presented as mean and standard error (bars), with statistical significance denoted by lines and asterisks ($p=0.010$). * $p<0.05$.

than 1 ng/ml) in plasma from normal subjects²⁰. The average of baseline serum histamine level of 19 patients with CU was 44.600 ± 3.818 ng/ml, and after four weeks of histamine-free diet, the serum histamine level was 16.650 ± 1.623 ng/ml. This reduction was statistically significant ($p=0.010$) (Fig. 4). Of the 19 patients with CU in our study, the baseline plasma DAO activity was 110.888 ± 53.910 (mIU/ml), and after four weeks on the histamine-free diet, it was 133.967 ± 51.724 (mIU/ml). According to the literature, DAO activity lower than 3 U/ml was considered decreased²¹. Serum DAO activity <10 U/ml was the threshold suggested as a cutoff for probable histamine intolerance²². Compared with the known normal range of DAO activity, the baseline DAO activity of 19 patients with CU was lower, but the difference after four weeks of histamine-free diet was not statistically significant ($p=0.165$) (Fig. 5).

Correlation between plasma histamine concentrations, diamine oxidase activity and symptom severity score

In 19 subjects, the relationship between changes in DAO activity and plasma histamine concentrations showed no statistical significance, when evaluated by Kendall or Spearman correlation ($p=0.325$ and $p=0.200$, respectively). In the same way, the relationships between changes in USS or UAS and plasma histamine concentrations also showed no statistical significance ($p=0.927$, $p=0.946$ and $p=0.114$, $p=0.130$, respectively). The relationships between changes in DAO activity and USS or UAS were also evaluated in the same manner, and all of them were not statistically significant ($p=0.160$, $p=0.195$ and $p=0.169$, $p=0.228$, respectively).

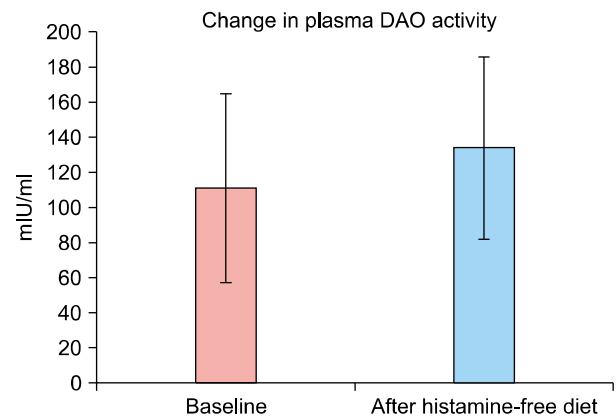


Fig. 5. Change in plasma diamine oxidase (DAO) activity after a 4-week histamine-free diet: Data are presented as mean and standard error (bars) ($p=0.165$).

DISCUSSION

The aim of the present study was to evaluate the changes of plasma histamine concentration and DAO activity in CU patients before and after a histamine-free diet. In the present study, we found histamine plasma levels in CU patients were diminished after four weeks of a histamine-free diet¹². This finding suggests that histamine plasma levels are dependent on diet in patients with CU¹². In this study, there was no significant decrease in the number of pills of antihistamine after histamine-free diet; however, the severity of symptoms, base on questionnaires had been changed¹². Compared to our previous study, we tried to make the histamine-free diet menu individually suitable for each patient and more applicable to Koreans¹². CU is a mast cell-dependent disease of mostly unknown cause²³. Mast cell mediator release has been shown to be the major common feature of all cutaneous whealing, and even though a number of potential mediators might be released from mast cells during this process, histamine seems to play a major role. This is because the whealing can be largely suppressed by drugs directed against the H1 type histamine receptor²³.

Many people think that foods are the reason or an aggregating factor and therefore undergo inappropriate food restriction^{24,25}. Some of them suffer nutritional imbalance and decline in quality of life due to inappropriate food restriction. However, with CU, food allergy is known to be a rare cause. It is reported in less than 2% of cases, food itself or food additives are the reason for CU²⁶.

Many reports have suggested associations between CU and histamine, or histamine intolerance, but not many prospective studies have been performed^{5,9,10,13,14,27}. Wantke et al.⁵ and Metcalfe²⁷ reported that an ologiant-

genic and histamine-free diet, respectively, induced significant clinical improvement in patients with CU. Also, additive- and preservative-free diets have been shown to improve clinical symptoms of CU⁹. In Guida et al.'s study¹⁰, the disappearance or reduction of symptoms after the histamine-free diet appeared to be correlated with lower histamine plasma levels. Additionally, in Wagner et al.'s study¹⁴, a total of 75% of the patients had a benefit from the low-histamine diet while DAO activity remained stable.

Increased levels of skin histamine have been reported in patients with CU²⁸. Also, increased histamine plasma levels have been reported in CU^{10,12}. In addition, Kanny et al.⁷ reported that plasma histamine levels were significantly higher after digestive histamine challenge in patients with CU, compared with controls. Especially in the kinetics of histamine, two groups showed significant difference. In the control population, the plasma histamine level was lowered as time passed, but in patients with CU, there was no significant difference between plasma histamine levels as time passed. A reduction of the intestinal barrier against chemical compounds (e.g., histamine) contained in some foods is hypothesized as a pathogenic mechanism of pseudoallergic reactions to food in CU²⁹.

It is suggested that increase in plasma histamine corresponds either to abnormal passage of histamine across the duodenal mucosa due to intestinal hyperpermeability, or to a deficit in the enzyme systems of histamine degradation¹². A defect in the activity of the enzymes (DAO) that catabolize histamine can explain the increased passage of histamine into the circulation in subjects with CU³⁰. In the study of Manzotti et al.²², the mean value (\pm standard deviation) of DAO activity in the cohort of patients with histamine intolerance symptoms was 7.04 ± 6.90 U/ml compared to 39.50 ± 18.16 U/ml in 34 healthy controls ($p=0.0031$). This means that, in patients with symptoms triggered by histamine-rich food, measuring the serum DAO activity can help identify subjects who could benefit from a histamine limited diet and/or DAO supplementation²². Properly designed, controlled studies investigating histamine intolerance that include histamine provocation are indispensable for providing insights into the area of food intolerance²².

In previous studies, DAO activity lower than 3 (U/ml) was considered decreased²¹ and lower than 10 (U/ml) was considered probable histamine intolerance²². Therefore, the baseline DAO activity of 19 patients with CU was significantly lower in this study. It should be noted that this study might be limited in that the presence of GI symptoms, or its severity, in our patients was not investigated, even though GI symptoms are common symptoms of his-

tamine intolerance. In addition, in our previous study about the relation between plasma histamine and DAO in CU, CU patients did not show significantly lower DAO activity¹². A study by Wagner et al.¹⁴, fifty-five blood samples with CU patients were evaluated and only five patients (9%) showed DAO activity below 3 U/ml, suggesting histamine intolerance. There was also no significant change stated between DAO measurements after histamine-free diet. Large group studies will be required to elucidate the relationship between plasma histamine concentrations and DAO activity.

Inappropriate food restriction without medical evidence can lead to nutrient insufficiency. Children with food allergies were smaller for their age than controls, even when they received similar nutrient intakes. Therefore, nutritional evaluation is essential for the follow up of children with food allergies³¹.

The limitations of this study include the following. First, most patients had been taking antihistamines for so long that their plasma DAO activity could have been influenced by it. However, in our study, antihistamines for CU patients could not be discontinued. Also, each patient had different duration and dose of drug before the study. Second, the duration of the histamine-free diet was relatively short and the sample size was relatively small. To check the influence of diet or nutrient, the study period might need to be longer than four weeks. Study periods of oligoantigenic and histamine-free diet or pseudoallergen-free diet were different for three weeks, three months, six months or 12 months^{9,10,32}. Third, making individual histamine-free diet menus was difficult, so help was needed from the Department of Nutrition. Also, it was difficult to offer a personalized diet for Koreans, and this required professional dietary knowledge. However, the menu itself was not so difficult to follow. In the end, future controlled study is needed to confirm the role of histamine-free diet in CU.

In this study, after being on a histamine-free diet for four weeks, patients showed significant improvement in their symptoms and decreasing plasma histamine level. Even so, the doses of drugs being used could not be reduced and there was no significant change in plasma DAO activity. In other words, there was no correlation between plasma histamine level and DAO activity, or between plasma histamine level and clinical subjective severity scores.

Although this is an open study based on the hypothesis of high plasma histamine level and a deficiency or reduced activity of DAO in CU according to the previous data, patients with CU seem to have increased sensitivity to histamine so avoidance of histamine rich food could be effec-

tive to reduce symptoms from histamines. Because there are many adult CU patients who seemed to suffer symptoms related to foods in Korea, and because a histamine free diet is a harmless treatment, this study is meaningful as evidence of the value of a therapeutic histamine-free diet. Additional further studies with longer duration of strict histamine-free diets may be needed in patients who have been using the conventional drugs with adjusted dose and duration.

We evaluated the effect of a histamine-free diet for four weeks for 22 adult patients with CU. In this study, there were significant clinical improvements in urticaria severity and the plasma histamine level was significantly reduced after the histamine-free diet. Even if the number of drugs used was not reduced and plasma DAO activity was not changed, a histamine-free diet cannot be said to be ineffective because it has resulted in a USS or UAS change that can be linked to the quality of life of the patient. The significance of this study is that it provides practical confirmation of the effectiveness of safe adjuvant therapy without major side effects. Thus, a histamine-free diet can be considered an applicable additional therapy for CU.

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SUPPLEMENTARY MATERIALS

Supplementary data can be found via <http://anndermatol.org/src/sm/ad-30-164-s001.pdf>.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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Supplementary Table 1. The food ranking of histamine level studied by our previous study

Name: Regeister number: Gender: Age:
 *Histamine is one of the causes of urticaria. Below is schematic table showing the histamine level of each food. You are advised to avoid foods with high histamine level which is in the upper side of the column.

		Histamine level of food						
		Fishery products	Meat products	Eggs	Fermented food	Vegetables	Dairy products	Etc.
Higher level	Grilled anchovy Grilled pacific saury		Pork Grilled sausage and ham		Red pepper paste Soybean paste	Spinach Fermented radish kimchi		
	Grilled mackerel		Chicken			Fermented cabbage kimchi	Cheese	Toasted laver
	Grilled hairtail		Raw sausage and ham					
	Can of tuna Boiled ahcnovy Boiled shrimp							
50 ng/g	Dried anchovy Boiled pacific saury							Raw laver
	Grilled Spanish mackerel							
	Boiled hairtail		Grilled beef					
	Squid		Boiled beef					
	Boiled mackerel		Raw beef	Boiled egg		Carrot	Milk	
	Boiled Spanish mackerel			Raw egg		Onion		
Lower level						Raw cabbage and radish		

Be aware that fermented foods (ex. Soybean paste, red pepper paste, kimchi, yogurt, cheese) contain high level of histamine, and please avoid them.

Also, fast foods, tomato, nuts including peanut, alcohols including wine, green tea, chocolate, grape, banana, strawberry, citrus fruits such as lemon and orange should be restricted.