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**A Popular myth – low-histamine diet improves chronic spontaneous urticaria –
fact or fiction?**

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Running head: Histamine intolerance in chronic spontaneous urticaria

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Abstract

Background: Chronic spontaneous urticaria (CsU) is a frequent dermatological disease that might last for months or years with high impact on quality of life. Known causes are autoreactive phenomena, infections or intolerances, rarely IgE-mediated allergies. One third of CsU patients benefit from a low-pseudoallergen diet. Additionally, it is often discussed, that reducing histamine ingestion alone might improve clinical symptoms and quality of life in CsU-patients despite the uncertain role of the histamine-degrading enzyme diamine oxidase (DAO).

Objective: Aim of this study is to investigate the impact of low-histamine diet on symptoms and quality of life in patients with CsU.

Methods: Patients suffering from CsU accompanied by gastrointestinal symptoms were included in the study. They underwent low-histamine diet for at least 3 weeks. During the whole study, urticaria activity score (UAS) was recorded daily in a patient's diary. Quality of life was assessed during screening, baseline and post-diet visits by completing questionnaires (DLQI and CuQ(2)oL). Diamine oxidase (DAO)-activity was measured before and after elimination diet.

Results: 75 % of the patients had a benefit from the low-histamine diet. 34 of 56 patients (61 %) reached the primary endpoint of the study, an improvement of UAS 4 of ≥ 3 . Overall a significant reduction from 9.05 to 4.23 points ($p=0.004$) was achieved; the average reduction in a strongly affected subgroup was 8.59 points ($p<0.001$). DAO activity remained stable.

Conclusion: Low-histamine diet is a therapeutically useful, simple and cost-free tool to decrease symptoms and increase quality of life in CsU-patients with gastrointestinal involvement. Further research is needed to understand the role of diamine oxidase.

Introduction

Urticaria is one of the most common dermatologic diseases. There are two main subtypes, chronic spontaneous (CsU) and inducible (CindU) disease. Acute spontaneous urticaria (AsU) is distinguished from chronic spontaneous urticaria (CsU) – defined lasting longer than 6 weeks– by the duration of symptoms. In case of long lasting CsU, international guidelines recommend to search for possible triggers of the disease i.e. infections, autoreactivity, or pseudoallergens¹⁻⁵. But sometimes no trigger can be detected and patients may suffer from symptoms for months and years with relevant impact on quality of life^{6,7}. Referring to the guidelines, 2nd generation antihistamines (including an up dosing regimen), omalizumab, leukotriene antagonists or cyclosporine A are recommended as treatment for chronic spontaneous urticaria¹. Former studies could demonstrate that avoidance of pseudoallergens (eg. acetylic acid, aromatic compounds of food, artificial preservatives and dyes) may help to reduce disease activity^{8,9}. Moreover,

several studies showed that a low-pseudoallergen diet for at least 3-4 weeks reduces urticaria activity including pruritus and wheals^{10,11}.

During the last years it has been discussed, that a low-histamine diet may be sufficient to reduce urticarial symptoms and that the benefit of the low-pseudoallergen diet is mainly due to reducing histamine intake¹². The pathomechanism of histamine intolerance is not fully understood. Previous studies demonstrated abnormalities in histamine metabolism in patients with chronic urticaria. Intraduodenal histamine application provoked an attack in 64 % of patients¹³. Many patients with CsU complain of worsening of symptoms by consuming histamine-rich food, like red wine or matured cheese, but to our knowledge, until now no studies are available supporting these observations.

Due to these facts, we hypothesized that a low-histamine diet might improve symptoms and quality of life in patients with CsU comparable to a low-pseudoallergen diet.

In cooperation with a nutritionist, people were asked to run a low-histamine diet over at least 3 weeks (table 1). The survey was conducted by assessing the Urticaria activity score (UAS), calculated by combining pruritus intensity and the number of daily wheals in a score system¹⁴. In addition, quality of life questionnaires were obtained: using the Dermatological life quality instrument questionnaire (DLQI)^{15,16} established for dermatological diseases and the Chronic Urticaria Quality of life questionnaire (CU-Q(2)oL), an urticaria specific quality of life questionnaire¹⁷. Diamine oxidase (DAO), the enzyme disintegrating histamine, was measured before and after dieting.

Methods

Subjects

In two specialized urticaria centres in Germany (Darmstadt, Mainz), patients suffering from CsU for at least 3 months (average: 25 months), accompanied by gastrointestinal disturbances (e.g. meteorism or diarrhoea) were enrolled in the study. Patients with a medical history of other causes of gastrointestinal symptoms (i.e. lactose, fructose, sorbit or gluten intolerance, sorbitol malabsorption, already diagnosed histamine intolerance, IgE-mediated food allergy, M. Crohn, Colitis ulcerosa, infectious diarrhea etc.) were excluded. At screening (day -7 before starting the diet) 66 patients were enrolled. Starting with the screening day, patients continued their normal diet for another 7 days completing additionally a diary. After 1 week, 57 patients (excluding drop-outs and lost of follow up's) underwent at least 3 weeks of low-histamine diet. In one patient calculation of UAS4 score was not possible. Finally, 56 patients (42 women, 14 men) completed the whole study and were statistically analyzed. Urticaria activity score (UAS) was recorded daily from screening to after-diet visit. Additionally, quality of life was examined by questionnaires. Dermatologic quality of life index (DLQI) and Chronic Urticaria Quality of Life Questionnaire (CU-Q(2)oL) were determined at screening, baseline and after dieting. Diamine oxidase activity (DAO) was measured by REA (radio extraction assay, manufacturer: Sciotec DAO-REA[®]) in blood samples at baseline and after dieting. Patients were asked to take antihistamines only when needed. All antihistamines were allowed (cetirizine, levocetirizine, loratadine, desloratadine, rupatadine, fexofenadine, mizolastine, dimetinden), even an up dosing. No histamine liberating drugs were allowed.

Primary endpoint of the study was an improvement of the 4-day urticaria activity score (UAS4) of at least 3 score points during the last 4 days of the diet compared to baseline UAS4 (during the 4 days before starting the diet). Secondary endpoints were changes in quality of life by surveying the DLQI and the CU-Q(2)oL. Comedication and changes in headache or gastrointestinal discomfort as well as adverse events were recorded.

This study was conducted according to the Declaration of Helsinki and all patients provided written informed consent. Ethic approval from the two county ethics committees was obtained. For statistical analysis and figures SPSS 20.0 was used.

Diet and medication regimen

All patients received a list of allowed food, composed by a nutritionist in accordance to the recommendations for histamine intolerance of the German Society of Allergy and Clinical Immunology, (table 1) and a diary for documentation of their daily ingested food and symptoms. No dietary supplements such as vitamins, homeopathic substances, plant preparations, minerals etc. were allowed. Corticosteroids or medications for acute infection etc. were only approved if necessary and had to be documented. During the whole study the patients were asked to take antihistamines only if necessary.

Outcome measures

Disease Activity

The urticaria activity score (UAS) was assessed daily. UAS4 scores were calculated by summarizing the scores 4 days before starting the diet and during the last 4 days before the end of the diet. UAS refers to the main symptoms: severity of itching and quantity of wheals, including number of wheals (0=no symptoms, <20=1, 20-50=2, >50=3) and severity of pruritus (no=0, mild=1, moderate=2, severe=3)¹⁰.

Each symptom can achieve a maximum score of 3 per day, resulting in 6 points at most per day, i.e. a total score of 24 for 4 days (UAS4). The variation of the UAS4 score was measured by subtracting the final UAS4 score from the UAS4-Score at baseline.

The UAS4 was chosen since it was identical to the score system used in comparable studies with low-pseudoallergen diet^{10,11}.

Quality of life

At screening, baseline, and after the diet, patients completed the 10 questions of the Dermatological life quality instrument questionnaire (DLQI), resulting in a maximum score of 30^{15,16}. The chronic urticaria quality of life questionnaire (CU-Q(2)oL), a disease specific score comprising questions on disease activity, pruritus, wheals, and their impact on daily life activities, was calculated to a maximum score of 42¹⁷.

Modifications of DLQI and CU-Q(2)oL were measured by subtracting each score at the end of the diet from score points achieved at baseline.

Diamine oxidase (DAO)

Blood samples were taken at baseline and the post treatment visit. The human serum was stored frozen until the assay had been performed.

DAO-activity was determined by evaluating the reaction product. The substrate used was radiolabelled putrescine-dihydrochloride. The resulting delta1-pyrroline, also containing the radiolabel, was separated from the matrix by liquid extraction. Afterwards a scintillation fluid was added to the organic phase containing the labelled delta1-pyrroline and radioactivity was determined in a beta-counter. The radioactive signal is directly proportional to the activity of DAO in the blood sample.

According to reference ranges DAO activity was interpreted as follows:

DAO < 3 U/ml	histamine intolerance accepted
DAO > 3 and < 10 U/ml	histamine intolerance probable
DAO > 10 U/ml	histamine intolerance unlikely

Results

Urticaria Activity

Three weeks of a low-histamine diet resulted in a significant reduction of the average UAS4 from 9.05 (\pm 6.11) to 4,23 (\pm 4.47) ($p=0.004$) in all patients. An improvement of urticaria activity score comparing baseline to post diet could be achieved in 42 out of 56 patients (75%), in 9 patients (16%) no change of disease activity was observed and in 5 patients (9%) symptoms worsened. The primary endpoint of the study,

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improvement of at least 3 points in urticaria activity score, was reached by 34 patients out of 56 (61%). Considering those patients, who accomplished the primary endpoint (n=34), the average reduction of the UAS4 was 8.59 points (median=9, p<0.001). Regarding a subgroup of patients (n= 31) with a higher disease activity at baseline (UAS \geq 9), the response to a low-histamine diet resulted in reduction of UAS4 score of 8.58 points (median = 9; p<0.001) (Fig. 1).

Quality of life

DLQI

Secondary endpoint of the study was an increase of life quality by decreasing DLQI of at least 2.5 score points from baseline to post-treatment. Questionnaires of 51 patients could be evaluated. The average reduction from baseline to post-treatment was 2.08 score points (mean) in all subjects. Regarding the subgroup with an UAS4 improvement \geq 3 score points, the average DLQI improvement was 3.83 (mean). Total number of analyzable questionnaires was 30 (out of 34 patients). Analyzing the subgroup of subjects with an UAS4 score of \geq 9 at baseline (n = 31), 27 questionnaires out of 31 could be evaluated. DLQI-score showed an improvement of 3.26 points. (Fig. 2).

CU-Q(2)oL

52 questionnaires concerning CU-Q(2)oL comparing baseline to post-diet could be evaluated and showed an average reduction from 5.46 score points, being statistically relevant (p \leq 0.01). The subgroup of subjects with an UAS4 improvement

≥ 3, showed a reduction of 8.32 (mean; n=31) from baseline to post treatment. Patients suffering severely from urticaria at baseline (UAS4 ≥ 9, n= 28), CU-Q(2)oL improvement from baseline to post-treatment was 6.14 (mean). Regarding scores at screening in comparison to post diet, the decrease of the score was even higher: from 37.04 (mean) at screening to 24.14 score points at post-treatment visit (53 questionnaires analyzable).

DAO-Activity

55 blood samples could be evaluated, showing a DAO-activity > 10 U/ml in 31 patients (56.4 %). 19 subjects (35 %) demonstrated activity values between 3 and 10 U/ml and 5 patients (9%) below 3 U/ml, suggesting histamine intolerance. No significant change could be stated between DAO baseline measurements 17.79 (mean; n=55) and values obtained after dieting: 17.01 U/ml, (mean; n=43). Regarding the responding subgroup (UAS4>3 reduction), an average reduction of DAO of 1.74 (mean; n=23) could be stated. Patients with UAS4 symptom score ≥ 9 at baseline (n=22) showed a decrease of 2.17 U/ml (mean) of DAO activity during study.

Antihistamine intake

This was a non-interventional study. The patients were instructed to take there antihistamines only if needed starting in the screening period during the whole study. 32 of 56 (57%) patients took antihistamines before the diet. The reduction in this population was 1.81 tablets/day: 22 of 56 (39%) reduced the intake of

antihistamines, 12 of those 22 stopped taking antihistamines during the study, in 8 of 56 (14%) the intake of antihistamines increased. The average reduction of antihistamine intake (cetirizine, fexofenadine, ebastine, desloratadine, rupatadine or dimetinden) after diet in the whole population was 0.93 tablets/day (n=56).

Discussion

Low-histamine diet decreased symptoms and increased quality of life in patients with chronic spontaneous urticaria. Additionally an overall reduction of antihistamine intake of almost 1 tbl/per day could be observed after dieting.

The primary endpoint, reduction of the UAS4 (>3 points) during diet was achieved comparable to studies run with low-pseudoallergen diet. Although low-histamine diet shows overlapping diet recommendations to low-pseudoallergen diet, a larger variety of food is permitted in low-histamine diet and it is easier to perform for patients. Sixty-one percent of the participating patients benefited from the diet. Of course the impact of spontaneous remissions should not be forgotten. The prognosis of chronic urticaria in a new observational, prospective study in order to investigate control status and remission rate showed a remission rate of only 2/59 patients (3.4%) in 6 months observation, by stepwise treatment (antihistamines, leukotriene antagonists, cyclosporine A, steroids) ¹⁷. In this cohort patients already suffered from CsU 25 months in average and the reduction of the UAS4 score seems to be due to the diet underlined by the fact that a decrease of antihistamine intake could be observed. Additionally quality of life improved during the diet. Even patients with higher severity (UAS4>9) had the same benefit. Low-histamine diet is an effective, easy to handle, cost-free and simple tool to improve disease activity in patients with CsU and

gastrointestinal symptoms and may be recommended for a period of three to four weeks to improve symptoms of CsU. These findings are comparable to studies performed with low-pseudoallergen diet in patients with CsU, which is effective in 31-71 % of the cases^{10,11,18}. In fact, reduction of pseudoallergen uptake in urticaria patients helps to diminish symptoms due to several mechanisms, one of them appearing to be the reduction leukotriene levels¹⁹.

The intake and metabolism of histamine plays a major role in patients with chronic urticaria^{20,21}. Whereas healthy subjects tolerated an intestinally applied dose of 120 mg histamine, patients with chronic urticaria developed an attack in almost 2/3 of the cases¹³. Urinary excretion of histamine is increased after higher intake of histamine in patients with CsU¹². Unspecific, non-IgE-mediated stimulus with A23187, FMLP and PAF showed no differences in histamine-release by skin mast cells or basophils in patients with CsU compared to healthy controls⁹. Non IgE- or IgG-dependent factors in sera of patients with chronic urticaria seem to be able to degranulate mast cells, although the exact nature of these histamine-releasing factors remains unclear^{20,21}. Guida et al.²² found an improvement of symptoms in CsU patients, who underwent an oligoantigenic and histamine-free diet in correlation to lower histamine plasma levels after the diet. They could not differentiate whether clinical improvement was due to low levels of histamine or the oligoantigenic part of the diet carried out during their study. In accordance to those findings, we presume, that symptoms of CsU patients in our study improved by reducing daily histamine intake alone. The observed effect may be explained by a barrier dysfunction in patients with chronic urticaria²³. Buhner et al.²⁴ measured gastroduodenal and intestinal permeability by sucrose i.e. lactulose/mannitol uptake, which improved in 29 out of

55 patients with chronic spontaneous urticaria after 24 days of pseudoallergen-free diet.

According to these findings, histamine level and its degradation seems to be of major concern in disease activity. Pollock et al.²³ could show differences in histamine metabolism in non-atopic urticaria patients and atopic patients. Endogenous histamine release and ingested histamine is discussed to be responsible for urticaria symptoms. This study offers an complementary additional, easy to perform diet as useful treatment option in CsU patients in order to reduce symptoms and antihistamine intake.

Interestingly diamine oxidase activity, the histamine degrading enzyme, which is often discussed as a biomarker in diagnosing histamine intolerance, remained stable before and after the diet. The slightly lower levels of DAO after diet could be a hint, that DAO was upregulated due to high histamine levels initially²⁵. Due to those results, DAO is not a recommendable biomarker in patients with CsU. Further investigations are necessary to prove the role of DAO in CsU.

Diet studies are always hard to run and difficult to start with a placebo-group. The study of a diet without a double-blind concept may result in a bias towards a benefit of the diet due to the placebo-effect. We decided not to enrole a subgroup with daily intake of histamine or a histamine provocation test, as the reproducibility of symptoms by oral uptake of histamine is a matter of discussion^{26,27} and may occur time-delayed²⁷. The amount of histamine inducing symptoms seems to vary already in healthy controls²⁷. In our opinion, continuous availability of histamine in patients with CsU, contributes to a higher reactivity of mast cells.

Histamine in plasma was not determined because it has no significant effect on symptom severity score in CsU²⁸.

Quality of life showed an improvement by a low-histamine diet, which was surprising, because dieting may decrease quality of life. According to our results, estimation of quality of life in patients suffering from CsU seems to be more reliable using the CU-Q(2)oL. We had our focus on DLQI to compare the results to former studies with low-pseudoallergen diet. In both questionnaires, impact on quality of life was higher during screening visit compared to baseline. This known phenomenon might be explained by the attention patients with chronic symptoms experience in a clinical trial. Evaluation of quality of life during a diet is influenced by the possible benefit and the suffering from a diet. Overall it increased more under diet conditions in patients with severe CsU.

In conclusion, low-histamine diet might be recommended for a period of 3-4 weeks in CsU patients in order to reduce symptoms and antihistamine intake as well as to improve quality of life. Further studies with control groups should show, if CsU patients show a benefit running low-pseudoallergen and/or low-histamine diet. According to these results, in our outclinics, a low-histamine diet is proposed to patients with CsU as an additional, easily to perform option in order to reduce symptoms and antihistamine intake.

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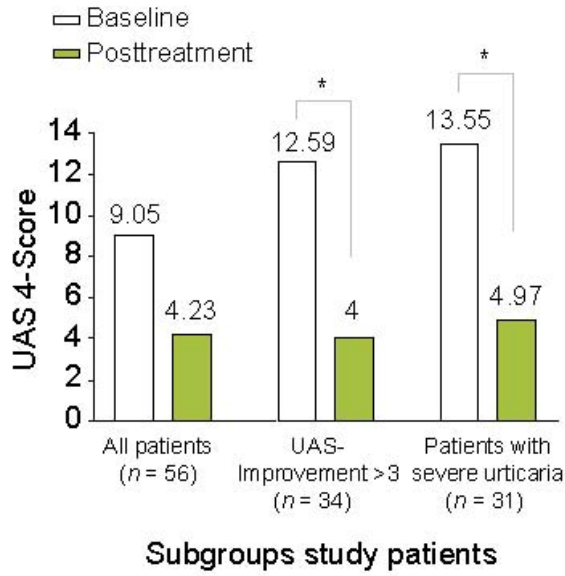
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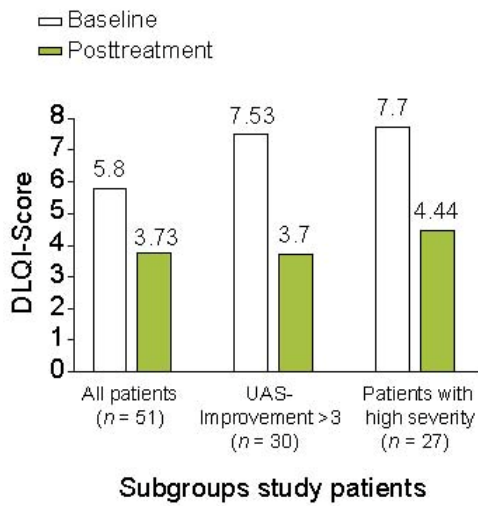
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Table 1: Recommended food in histamine-reduced diet

Dairy products: milk, cream and sour cream, butter milk, cream cheese, soured milk, curd cheese	Meat and eggs: eggs, cooked ham, not cured beef, veal, pork, lamb, chicken
Fish (fresh or fresh frozen): plaice, coalfish, codfish, haddock, trout, hake, perch	Spread: butter, margarine, honey, home made jam (permitted fruit only)
Sweets and Goodies: fruit drops, fruit gums, chewing gum, popcorn	Desserts: cold sweet soup, rice pudding, stewed fruit*, sorbet and ice cream, fruit yoghurt or curd cheese with fruit*, vanilla custard *(permitted fruit only)
Fruits: everything, except for strawberries, raspberries, citrus fruit, bananas, kiwis, plums, papaya	Vegetable: Any fresh or frozen vegetable, except for tomatoes, spinach, avocados, egg plant
Cereals/Potatoes/Noodles: bread and pastries, pasta, all kind of potatoes, cereals, grains (rice, corn, millet seed, buckwheat)	Beverages: Soda water, home made fruit and vegetable juices* *(permitted fruit only)



UAS 4-Change (in Score-Points)	
	Mean value
All patients	4.82
Improvement >3	8.59
Patients with severe urticaria	8.58



DLQI-Change (in Score-Points)		
	Median	Mean value
All patients	1	2.08
Improvement >3	2.5	3.83
Patients with high severity	2	3.26