

Effects of low pseudoallergen diet on urticarial activity and leukotriene levels in chronic urticaria

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Abstract Pseudoallergens and leukotrienes (LTs) may have a role in chronic urticaria (CU). The aim of our study is to evaluate the response to the low pseudoallergen diet therapy in patients with CU and the change in LT levels in diet responsive and non-responsive patients. 34 patients with CU were put on diet for 4 weeks. All patients kept a daily score sheet of pruritus and whealing symptoms. The urticarial activity score (UAS) of each patient was calculated with the sum of pruritus and wheal score. The sum score of the first 7 consecutive days (UAS7-first week) and last 7 days (UAS7-fourth week) were used to compare the clinical outcome of the diet. A reduction of $\geq 50\%$ in UAS7-fourth week compared to UAS7-first week was considered as “response”. Urinary LTE4 (uLTE4) level of each patient was measured at baseline and after the 4 week of diet therapy. 14 of the patients (41.2%) were responsive to diet therapy. Baseline uLTE4 levels were

similar between responsive and non-responsive patients ($P = 0.540$). Second uLTE4 levels (after the 4 week of diet therapy) were significantly lower in responsives than in non-responsive patients ($P < 0.001$). Second uLTE4 levels of responsives were significantly lower than the baseline values ($P = 0.019$), whereas this was not significant for non-respondives ($P = 0.070$). There was a significant correlation between the change in uLTE4 levels and the change in mean urticarial activity scores ($r = 0.554$, $P = 0.001$) in the whole study population. In conclusion, low pseudoallergen diet helps to reduce the urticarial activity in CU. The change in urticarial activity correlates with the change in LT levels.

Keywords Chronic urticaria · Leukotriene · Low pseudoallergen diet · Urticarial activity

Abbreviations

CU	Chronic urticaria
CysLT	Cysteinyl leukotriene
LPD	Low-pseudoallergen diet
LT	Leukotriene
NSAID	Non-steroidal anti-inflammatory drug
UAS	Urticarial activity score
UAS7-first week	Urticarial activity score at first week
UAS7-fourth week	Urticarial activity score at fourth week
Δ UAS	Change in urticarial activity score (UAS7-fourth week – UAS7-first week)
uLTE4	Urinary leukotriene E4
Δ uLTE4	Change in urinary leukotriene E4 (second urinary leukotriene E4 – baseline leukotriene E4)

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Introduction

Urticaria with spontaneous wheals and/or angioedema occurring for more than 6 weeks without external physical stimuli is called chronic urticaria (CU) [9]. The pathogenesis of CU is not well defined. Although mast cell degranulation and histamine release are known to occur, the eliciting factors are not clear. Since most of the patients remain symptomatic despite antihistamines, it is supposed that other mediators, such as kinins, prostaglandins, and leukotrienes (LT) may also constitute the appearance of the symptoms seen in CU [19].

Intolerance to pseudoallergens has been suggested to be a cause of chronic urticaria [27, 28]. Pseudoallergens are naturally occurring food ingredients, such as salicylates, aromatic compounds, and food additives. The proposed pathogenic mechanism in pseudoallergic reactions was considered to involve the LT pathway [4]. They trigger non-immunologically mediated urticarial flares that clinically resemble allergic reactions [27]. Unlike IgE-mediated reactions, no skin, or in vitro test is available in pseudoallergic reactions. Urticarial symptoms of patients with CU may improve when the daily diet of patients include low levels of pseudoallergens [28]. Various studies evaluating the therapeutic effects of low-pseudoallergen diet (LPD) in CU have been performed [2, 3, 7, 8, 10–12, 14, 15, 17, 18, 21–25, 27]. However, the effects of LPD on LT levels and relationship between LT levels and disease activity in patients with CU have not been investigated before. Hereby, we designed a prospective trial to evaluate (a) the response to the LPD therapy in patients with CU and (b) the change in LT levels in responsive and non-responsive patient groups.

Methods

Study participants

A cohort of 34 patients with CU (26 females, 8 males; mean age 40.88 ± 11.52 years; range 23–77 years) who presented to our dermatology out-patient clinic were invited to participate in the study. The group of patients included only those with daily symptoms of CU. Patients younger than 18 years, patients with urticaria associated with an underlying disease (systemic lupus erythematosus, hepatitis, Hodgkin's disease, vasculitis, renal or hepatic insufficiency, blood dyscrasia, malignancy, malabsorption, chronic infection, asthma, nasal polyp, drug or alcohol abuse, clinically significant psychiatric, cardiovascular, hepatic, neurological, endocrine, or other systemic disease), patients with predominant physical urticaria, urticaria due to medications, insect bites, food, or other known

aetiology, and patients with chronic non-steroidal anti-inflammatory drug (NSAID)/aspirin intake were excluded from the study.

The control group included 34 age and sex-matched healthy hospital employees (26 females and 8 males, mean age: 41.09 ± 11.75 years, range 24–78 years) who were willing to participate in the study. They had no symptoms or history of urticaria, NSAID/aspirin hypersensitivity, asthma, atopy, and any systemic disease. Neither female controls nor patients were pregnant or actively nursing.

The study was approved by the Ethical Committee of Hacettepe University Faculty of Medicine, conducted according to the Declaration of Helsinki. All participants gave written informed consent.

Study design

In a prospectively study design, all patients were given a LPD for 4 weeks after a 2-week run-in period. Each patient kept a symptom diary for a standardized urticarial activity evaluation. The urticarial activity scoring system (UAS) was used to determine the disease activity and response to treatment as defined in the guidelines [29]. Patients reported the severity of pruritus and number of wheals every day in the diary. Pruritus severity was rated on a scale of 0 to 3 (0 = none, 1 = mild, 2 = moderate, 3 = intense). The number of wheals was graded from 0 to 3: 0 = none; 1 = mild (<20 wheals/24 h); 2 = moderate (20–50 wheals/24 h); 3 = intense (>50 wheals/24 h or large confluent areas of wheals). The urticarial activity score of each patient was calculated with the sum of pruritus and wheal score. The sum score of the first 7 consecutive days (UAS7-first week) and the sum score of the last 7 days (UAS7-fourth week) were used to compare the clinical outcome of the LPD therapy. UAS scores ranged from 0 to 42.

A reduction of $\geq 50\%$ in UAS7-fourth week compared to UAS7-first week was considered as “response” (Study design is detailed in Fig. 1).

Diet and medications

All patients were given a standardized LPD for 4 weeks as previously described [27] after a nutritional consulting in the out-patient clinic. The diet used was the one originally used by Zuberbier [27] and not amended to a specific Turkish situation. Foods containing preservatives, artificial substances, or dyes and all kinds of industrially processed foods were eliminated. To ensure an optimal compliance and a standardized follow-up, patients were evaluated in weekly visits or interviewed on the phone every week by the same physician (GA). Patients were allowed to take antihistamines only for severe symptoms such as

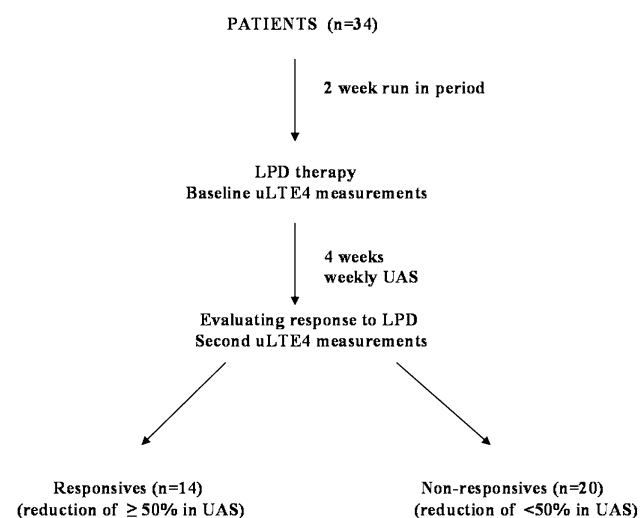


Fig. 1 Study design. *LPD* low pseudoallergen diet, *uLTE4* Urinary leukotriene E4, *UAS* urticarial activity score

intolerable itching, widespread wheals, and angioedema attacks. Only paracetamol was allowed for analgesia when required. All patients were re-evaluated and their records were checked at the end of the study.

Urinary LTE4 measurement

All participants avoided NSAID/aspirin for at least 2 weeks before and during the study. They were requested to refrain from laborious efforts during at least 2 days before collecting urine samples. Urine samples were obtained in the morning from all patients before the intervention and after the completion of the diet, from healthy controls once, and stored in -80°C until analysis. The urinary LTE4 (uLTE4) levels were measured by direct enzyme immunoassay (Cayman Chemicals, Ann Arbor, MI, USA). All measurements were done in a single run in accordance with the directions of the manufacturer. The results were expressed in picograms per milligram of creatinine.

Statistical analyses

Evaluation of normality was performed with the Kolmogorov Smirnov test. Normally distributed continuous variables were expressed as mean and standard deviation ($\text{mean} \pm \text{SD}$), and were compared with student's *t* test (for independent groups) or with paired samples test (for dependent groups). Non-normally distributed continuous variables were expressed as median and interquartile ranges 25 and 75 [median (IQR 25–IQR 75)], and were compared with Mann–Whitney *U* test (for independent groups) or Wilcoxon signed ranks test (for dependent groups). Categorical variables were compared with Pearson χ^2 or Fischer's exact test. The association between continuous variables was explored by Pearson (normally distributed) or Spearman (non-normally scattered) correlation analysis. All statistical analyses were performed using SPSS version 15.0 statistical software package (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of patients

All participants completed the study. A reduction of $\geq 50\%$ in UAS7-fourth week compared to UAS7-first week was observed in 14 (41.2%) patients, who were considered as responsive to LPD. The ages, gender, duration of the disease, number of patients with a history of previous angioedema attack, frequency of urticaria flares during last week before LPD therapy, and number of patients with previous antihistamine treatment were all similar between the LPD responsive and non-responsive patient group. The number of patients were previously on systemic steroid therapy were not different between responsive group and non-responsive group ($P = 0.135$). Table 1 shows the demographic and clinical characteristics of responsive and non-responsive groups.

Table 1 Demographic and clinical characteristics of responsive and non-responsive groups

Continuous variables are reported as mean $\pm$ SD for normally distributed data or median (interquartile range) for asymmetrically distributed data. Categorical variables are reported as number (%)

	Responsives (<i>n</i> = 14)	Non-responsives (<i>n</i> = 20)	<i>P</i>
Age (years)	41.6 $\pm$ 12.9	39.9 $\pm$ 9.6	0.655
Female, <i>n</i> (%)	12 (85.7)	14 (70.0)	0.422
Duration of disease (months)	16 (7–27)	24 (8–48)	0.419
Urticaria flares during last week before study (days per week)	7	7	0.990
History of angioedema attack, <i>n</i> (%)	9 (64.3%)	12 (60.0)	0.800
Previous antihistamine therapy, <i>n</i> (%)	13 (92.9)	19 (95.0)	0.999
Previous steroid therapy, <i>n</i> (%)	7 (50.0)	4 (20.0)	0.135

Table 2 Urticarial activity scores and urinary LTE4 levels in responsive and non-responsive groups

Variables	Responsives (<i>n</i> = 14)	Non-responsives (<i>n</i> = 20)	<i>P</i>
UAS7-first week	10.8 (15–23.5)	17.5 (13.3–25.0)	0.400
UAS7-fourth week	3 (0–8.8)	16.5 (13–24)	<0.001
Δ UAS	–11.5 [(–12.3)–(–9.3)]	–1 [(–4.5)–(1)]	<0.001
Baseline uLTE4 levels	800 (578–1,298)	775 (493–1,073)	0.540
Second uLTE4 levels	310 (255–605)	1,185 (675–1,798)	<0.001
Δ uLTE4	–570 [(–700)–(–30)]	245 [(–78)–(1,125)]	0.001

Continuous variables are reported as mean $\pm$ SD for normally distributed data or median (interquartile range) for asymmetrically distributed data. uLTE4 levels are expressed as pg/mg creatinine

LPD low pseudoallergen diet, uLTE4 urinary LTE4, Δ uLTE4 difference between the second and baseline uLTE4 levels, UAS7-first week urticarial activity score at first week, UAS7-fourth week urticarial activity score at fourth week, Δ UAS difference between UAS7-fourth week and UAS7-first week

Nine patients (64.3%) in responsive group and 16 (80.0%) in non-responsive group needed H1 receptor antagonists because of severe urticarial activities and angioedema attacks. The number of patients who required antihistamine therapy during the study period was similar between the responsive and non-responsive patient groups ($P = 0.435$).

Change in urticarial activity

The urticarial activity scores at first week (UAS7-first week) was similar between responsive and non-responsive groups [median: 10.8 (15–23.5) vs. 17.5 (13.3–25.0); $P = 0.400$]. At the fourth week, the UAS7 values of the responsive were significantly lower than non-responsive patients [median: 3 (0–8.8) vs. 16.5 (13–24); $P = <0.001$]. In the responsive group, UAS7-fourth week was significantly lower than UAS7-first week [median: 3 (0–8.8) vs. 10.8 (15–23.5); $P = 0.001$]. In the non-responsive group, there was no difference between UAS7-first week and UAS7-fourth week [median: 17.5 (13.3–25.0) vs. 16.5 (13–24); $P = 0.264$]. When the differences between UAS7-fourth week and UAS7-first week (Δ UAS = UAS7-fourth week – UAS7-first week) was analysed, Δ UAS of the responsive patients were significantly lower than Δ UAS of the non-responsives [median: –11.5 [(–12.3)–(–9.3)] vs. –1 [(–4.5)–(1)]; $P = <0.001$] (Table 2).

Urinary LTE4 levels

Baseline uLTE4 levels were similar between responsive and nonresponsive patients [(median: 800 (528–1,298) vs. 775 (493–1,073) pg/mg creatinine; $P = 0.540$]. After the 4 weeks of intervention period, second uLTE4 levels were significantly lower in responsive group than in nonresponsive group [(median: 310 (255–605) vs. 1,185 (675–1,798) pg/mg creatinine; $P < 0.001$] (Table 2).

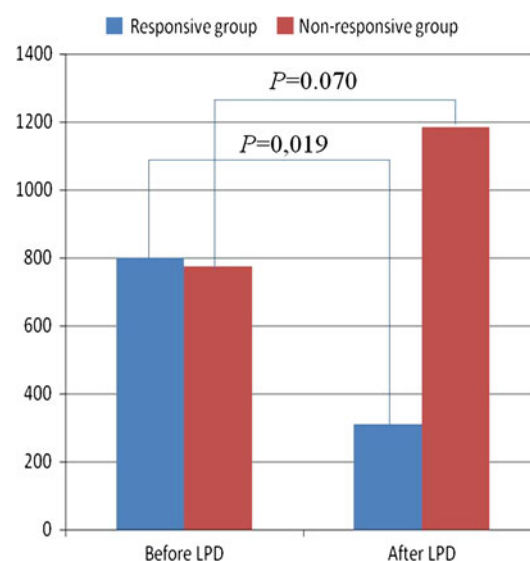


Fig. 2 Urinary LTE4 levels (uLTE4) before LPD and after LPD in responsive and non-responsive patient groups. LPD low pseudoallergen diet

In responsive group, uLTE4 levels significantly decreased from baseline values after 4 weeks of intervention period [baseline uLTE4 median: 800 (578–1,298) vs. second uLTE4 median: 310 (255–605) pg/mg creatinine ($P = 0.019$)]. In non-responsive patients, there was no significant difference between baseline and second uLTE4 levels [baseline uLTE4 median: 775 (493–1,073) vs. second uLTE4 median: 1,185 (675–1,798) pg/mg creatinine ($P = 0.070$)] (Fig. 2).

Mean change in uLTE4 levels (Δ uLTE4 = second uLTE4 – baseline uLTE4) was significantly higher in the non-responsive group compared to responsive group [245 [(–78)–(1,125)] vs. –570 [(–700)–(–30)], $P = 0.001$] (Table 2).

Since Δ uLTE4 values increased from responsive to non-responsive patient group, a correlation analysis was

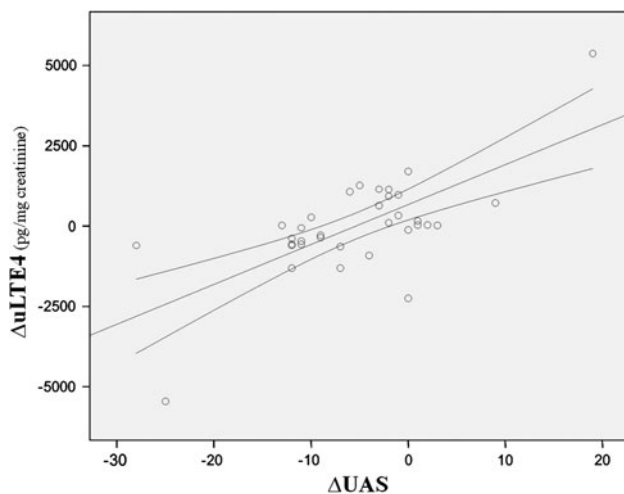


Fig. 3 Correlation between change in urinary LTE4 levels ($\Delta u\text{LTE4}$ = second $u\text{LTE4}$ level – baseline $u\text{LTE4}$ level) and change in urticarial activity scores [ΔUAS = UAS7 -fourth week – UAS7 -first week] in the study group ($r = 0.554$, $P = 0.001$)

performed between $\Delta u\text{LTE4}$ and change in UAS (ΔUAS = UAS7 -fourth week – UAS7 -first week). There was a significant correlation between $\Delta u\text{LTE4}$ and ΔUAS indicating that a reduction in disease activity was closely correlated with a decrease in $u\text{LTE4}$ levels and vice versa ($r = 0.554$, $P = 0.001$, Fig. 3).

Discussion

Many studies about pseudoallergen elimination diets in urticaria have been performed [2, 3, 7, 8, 10–12, 14, 15, 17, 18, 21–25, 27] with a range of 27.8–93.0% positive responses. The wide range of positive response may depend on differences in study designs, patient characteristics, durations of diets, and diet contents in these studies. In our study, patients with only daily symptoms were included. The majority of previous studies investigating the effect of LPD on chronic urticaria did not include patients with daily symptoms or they did not mention the urticarial activity of the patients in detail. Therefore, higher or lower response rates to LPD may be due to different profiles of urticarial activity in these studies. Recent studies are more detailed about study designs, contents of diets, clinical evaluation criteria and analysis of the results [2, 3, 12, 27]. Nevertheless, it is not possible to compare the response rates of these studies since there are not standardized criterion/criteria for defining “response”. Zuberbier et al. [27] reported that a positive response (reduction of daily symptoms including wheals and angioedema) of 73% was achieved after a 3-week pseudoallergen-free diet. In the study of Buhner et al. [3], 52.7% of CU patients benefited from a 24-day LPD. More than 50% reduction of scores

(with wheal and pruritus scores) was defined as response. Bunselmeyer et al. [2] administered a 5-week pseudoallergen-free diet, which caused improvement (reduction of severity of symptoms and increase in quality of life) in 68% of patients with CU. Last, Magerl et al. [12] evaluated the response with improvement in urticarial activity score (with wheal and pruritus scores) and dermatology life quality index. 28% of patients were defined as strong and partial responders. In our study, patients were on a 4-week LPD and evaluation of response depended on urticarial activity score that included wheals and pruritus scores. The overall reduction of $\geq 50\%$ in UAS was detected in 14 of all study patients (41.2%) as a response.

In our study, some patients needed adjuvant antihistamine intake during LPD since therapy with LPD alone was not sufficient to control the disease activity. The use of antihistamines encouraged the patients to continue the LPD therapy and to complete the study period. Furthermore, because of similar numbers of patients requiring antihistamines in responsive and non-responsive groups, the clinical outcomes of two groups could be compared. In the previous studies, only clinical responses of the patients on LPD were evaluated. However, in our study, we also analyzed the changes in LT levels. To date, there has been no study investigating the effect of LPD treatment on leukotrienes.

Leukotrienes are a family of polyunsaturated lipoxigenated eicosatetraenoic acids that are derived from arachidonic acid and exhibit a wide range of biological effects [1]. Cysteinyl LTs (CysLTs) are the major players in the complex cascade of allergic reactions. The final metabolic product of CysLTs is LTE_4 , which is excreted in urine [6]. Urinary LTE_4 levels reflect the global CysLT biosynthesis. The studies evaluating the role of CysLT metabolism in CU demonstrated higher $u\text{LTE}_4$ levels in patients with CU than healthy individuals [12, 26]. Leukotriene pathway was also suggested to involve in the mechanism of pseudoallergic reactions in CU [4, 13]. Food additives produced increase in $u\text{LTE}_4$ levels in patients with CU and food additive hypersensitivity [4]. When antihistamines failed to be effective in CU with hypersensitivity to food additives and/or aspirin and in CU, which is resistant to antihistamines, addition of antileukotriene treatments, provide improvement of symptoms [5, 6, 13, 16, 20].

In the present study, the baseline LT production was similar between the responsive and non-responsive patients before administration of LPD. After 4-week LPD therapy, the LT levels decreased in responsive patients. The second LT levels of responsives were also lower than non-responsives. In contrast, the LT levels of non-responsive patients increased when compared to their baseline values. Furthermore, disease activity was closely associated with $u\text{LTE}_4$ levels. Depending on these findings, it may be

speculated that LPD may decrease the disease activity of responsive patients via decreasing LT levels of these patients. In patients who are non-responsive to LPD, increased urticarial activity may be associated with overproduction of LTs. In this situation, there may be other factors rather than pseudoallergens, which affect the disease activity via LT pathway. To suppress the effects of LTs in patients who do not benefit from LPD, additional antileukotriene therapies may produce regression and control of the urticarial activity. Future studies investigating the outcomes of adjuvant antileukotriene therapies to LPD in CU are needed.

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Conflict of interest None.

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