

ORIGINAL ARTICLE

Exploring gluten sensitivity in chronic spontaneous urticaria

Gluten sensitivity in CSU

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Summary

Background. Chronic spontaneous urticaria (CSU) is a common, challenging condition, usually impairs patients' quality of life. While current medications are mainly symptom-based, many people still suffer. There is limited and inconclusive evidence suggesting a possible role of gluten sensitivity in CSU, and current international guidelines do not recommend a gluten-free diet as a standard therapeutic approach. This study aimed to assess the effect of a gluten-free diet (GFD) on CSU activity.

Methods. This one-arm sequential interventional study was conducted on 89 CSU patients at Ain Shams University Hospitals. Celiac patients were excluded, and only patients with negative anti-TTG were allowed. Participants underwent a skin prick test for wheat and gluten. They followed a GFD for three weeks, after which gluten was reintroduced, and patients were reassessed over an additional short-term follow-up period of about one week. Urticaria Activity Score 7 (UAS7) was used to evaluate severity. Laboratory investigations were conducted. **Results.** After three weeks on GFD, forty-three patients (48.3%) showed improvement in urticaria activity following gluten elimination and subsequent symptom worsening after gluten rechallenge. This was documented by UAS7 score which varied significantly ($p < 0.001$). CRP was significantly higher among the non-gluten sensitive group; other laboratory parameters were comparable. **Conclusions.** Gluten elimination was associated with reduced

urticaria activity in a subset of patients with CSU. However, controlled studies are needed to establish its efficacy.

KEY WORDS

Chronic Spontaneous Urticaria, Gluten Sensitivity, Urticaria Activity Score, Gluten-Free Diet, Rechallenge.

IMPACT STATEMENT

Nearly half of seronegative chronic spontaneous urticaria patients improved on a gluten-free diet and relapsed after rechallenging. A dietary trial may identify responsive patients and complement guideline-based therapy.

Introduction

Chronic spontaneous urticaria (CSU) is a distressing skin disorder characterized by the spontaneous appearance of wheals and angioedema, or both, persisting for more than six weeks (1). Attacks may occur daily or intermittently, with unpredictable flare-ups and periods of remission that can last months or even years (2). The erratic course of CSU significantly impacts patients' quality of life, causing physical discomfort, sleep disturbances, and emotional distress (3). This disease is burdensome, as its prevalence is estimated to range between 0.5% and 1% in the general population (4). Moreover, it is more predominant among middle-aged females (3).

CSU results from mast cell degranulation, which leads to plasma extravasation into the dermis and subsequent hive formation. Histamine acts as the main mediator, along with other inflammatory mediators contributing to disease. Despite being a common disease, the underlying mechanisms and triggers that lead to this degranulation are still unrevealed in most cases. Researchers have shown an increased interest in studying such a topic and hence many theories were suggested, including autoimmunity, autoallergy, and inflammation. (3).

Current treatment options for CSU aim at symptom control rather than disease modification. International guidelines recommend a stepwise approach, starting with H1-antihistamines at standard or high doses, followed by biologics like omalizumab or immunosuppressants like cyclosporin for

refractory cases (2). However, up to 61% of CSU patients remain unresponsive to standard antihistamine therapy (5). While omalizumab and cyclosporin have demonstrated efficacy, their high cost and limited accessibility impose a significant economic burden on patients. Furthermore, approximately 25% of patients fail to achieve complete remission even with omalizumab, highlighting the need for alternative therapeutic approaches (6).

Gluten-related disorders, including celiac disease (CD) and non-celiac gluten sensitivity (NCGS), have been associated with various dermatologic conditions. For example, Dermatitis herpetiformis is strongly associated with CD and amazingly improves on a gluten-free diet (GFD) (7). Also, there is some evidence that skin psoriasis, especially in patients with CD may improve on avoiding gluten too; however, few experts believe that even psoriatic patients without CD may benefit, as they may have asymptomatic gluten intolerance (7). In some cases, urticaria symptoms have been reported to improve with a gluten-free diet (GFD), particularly in chronic presentations (7). Whether this is related to an allergic condition to gluten or not is still uncertain. Therefore, this study aims to assess the impact of a gluten-free diet on CSU activity.

Patients and methods

Design and population:

This prospective, single-arm interventional study was conducted on patients attending the Allergy Clinic at Ain Shams University Hospitals between March 2024 and September 2024. A total of 125 CSU patients were initially enrolled in the study, but 20 lost follow-up, and 16 did not adhere to the GFD, only 89 completed the study. **Figure 1.** The study was approved by the Research Ethics Committee of the Faculty of Medicine, Ain Shams University (Approval code: MS434/2022, Approval date: 02/07/2024), and all participants provided informed consent.

Eligibility criteria

Participants were adults aged 16–60 years diagnosed with chronic spontaneous urticaria as per EAACI guidelines (wheals and/or angioedema for >6 weeks) (2, 8). Exclusion criteria were patients with chronic diseases (hepatic, renal, malignancy, or autoimmune disorders), pregnancy or lactation, and those already diagnosed with celiac disease. Also, patients with chronic inducible urticaria alone were excluded.

Assessments

Detailed history was taken from all patients, activity was assessed by Urticaria Activity Score (UAS7), which quantifies daily wheals and pruritus (scored 0–3 each) over seven days, with a maximum score of 42 (9). A full clinical examination was performed, recognizing that wheals and angioedema are transient; therefore, patient documentation, including symptom records and images, was reviewed. Wheals, being evanescent and itchy, were confirmed by history in all patients.

Skin prick test

Skin prick testing (SPT) for wheat/gluten was performed using standardized allergen extracts at the Ain Shams University Laboratory. Antihistamines were discontinued at least five days before testing. Allergen extracts were prepared as aqueous wt/vol solutions; a 1:100 potency indicates 1 g of dry allergen per 100 cc phenol-saline buffer, followed by elution and filtration.

A wheal diameter ≥ 3 mm was considered positive. Test was done on the volar surface of the forearm. A drop of the reagent, along with saline (negative control) and 10 mg/ml histamine solution (positive control) were placed on the skin and instantly pricked by a single-head metal lancet superficially. Result was checked in 20 minutes. Positive result is when the wheal of the test is similar in size or bigger than that of histamine (9).

Laboratory:

Routine blood tests and immunological assessments were done. Venous blood (4 mL) was collected aseptically, processed for serum separation, and stored at -20°C . Tests included CBC (Sysmex XNXX1000), ANA (immunofluorescence, DiaSorin, USA), C-reactive protein (CRP), creatinine, uric acid, liver function tests (COBAS C6000, Roche, Germany), total IgE (ELISA, DRG GmbH, Germany), and anti-TTG IgA (chemiluminescence, BioFlash). Low anti-TTG IgA values were confirmed by assessing total IgA. Patients with low total IgA underwent testing for antiTTG IgG too. All procedures followed manufacturer instructions.

Serum anti-TTG IgA was measured using an ELISA reader, and TTG IgA concentrations were reported in international units (IU/mL). Positive TTG IgA was ≥ 30 IU/ml.

The questionnaire used to collect information on patient concomitant symptoms covered several domains, including the frequency and severity of symptoms, possible triggers including gluten,

regular medications, gastrointestinal symptoms, and symptoms related to celiac disease. In addition, wheat preference and the frequency and amount of wheat product intake was also demanded. The questionnaire, initially in English, was administered by the doctor at the allergy clinic during the first visit, with the doctor filling it out based on patient responses. Patients' dietary habits, concomitant symptoms, and potential triggers were recorded using a physician-administered questionnaire at the initial visit. Dietary adherence was assessed through a review of patients' food diaries **Figure 2**

All participants were instructed to follow a GFD for three weeks. Urticaria activity was assessed using the UAS7 at baseline and following the gluten-elimination period. Subsequently, gluten was reintroduced into the participants' diets, and they were reassessed during a short-term follow-up period of 3–7 days. UAS7 was reassessed following gluten rechallenge to evaluate changes in urticaria activity. Dietary adherence was monitored through patients' food diaries. All participants continued their regular CSU medications, including antihistamines and other prescribed therapies, without modification throughout the study period.

Statistical analysis

Data management and statistical analysis were done using SPSS version 27 (IBM, Armonk, New York, United States). Quantitative data were assessed for normality using the Shapiro-Wilk test and direct data visualization methods. According to normality, quantitative data were summarized as mean and standard deviation (S.D.) or median and interquartile range (IQR). Categorical data were summarized as numbers and percentages. Comparisons between groups were conducted using the Independent t-test for normally distributed variables and the Mann–Whitney U test for non-parametric data. Categorical variables were analyzed using the Chi-square test or Fisher's exact test, as appropriate. Repeated measures ANOVA test was used to compare the changes in UAS7 scores at baseline and after gluten elimination and rechallenge within each group. P-value ≤ 0.05 was considered indicative of statistical significance.

Results

This study encompassed 89 CSU patients after excluding those who lost follow up or could not maintain on GFD. The mean age of them was 33.37 +/- 10.68 years, where 68 (76.4%) of them were females. The median disease duration was 4 (1.4-7) years. Baseline UAS score was 33.58 +/- 8.45. After

reviewing main symptoms with patients, 42 (47.2%) patients suffered from angioedema, while 28 (31.5%) from flatulence and/ or unexplained attacks of diarrhea. The most relevant laboratory result was high CRP, where median was 11.00 (7.00-15.10) mg/dl. It is worth noting that TTG IgA was normal in all patients, total IgA was normal in all patients except only one showing a low value, and TTG IgG was normal for that patient. Further descriptive and laboratory data of patients is present in **Table I**.

After a 3-week GFD, 49 patients (55.05%) showed improvement in UAS7. Upon rechallenge, only 43 patients (48.31%) experienced significant worsening, 6 patients (6.74%) showed no change. And the rest of patients; 40 (44.94%) showed no significant change in UAS7 after GFD. So, 43 patients (48.31%) were labelled as GFD responder group and 46 patients (51.68 %) as non-gluten sensitive group (NGS).

UAS7 score differed significantly across the three-time points in the GFD responders group. UAS7 score after gluten elimination was significantly lower compared to baseline ($P < 0.001$). UAS7 score after rechallenging with gluten was significantly higher compared to the gluten elimination phase ($P < 0.001$) but remained significantly lower than the baseline score ($P < 0.001$). **Table II, Figure 3**

Baseline UAS7 score did not vary significantly between both groups (p value 0.57). However, it was significantly higher in the NGS group after gluten elimination (33.02 ± 9.06) compared to the GFD responder group (14.16 ± 9.72), (p value < 0.001). Interestingly, UAS7 score after rechallenging with gluten was also significantly higher in the NGS (33.02 ± 9.06) compared to GFD responder group (25.23 ± 8.79), (p value < 0.001). **Table II**

Table 1 also shows intergroup comparison between both GFD responder group and non-sensitive patients. They were comparable regarding demographic data. Nevertheless, regarding reported symptoms; flatulence and diarrhea were significantly more frequently reported in GFD responder group (58.1%) compared to NGS group (6.5%) and p value was < 0.001 . As regard laboratory results; median CRP levels were significantly higher in the non-gluten-sensitive group than in the GFD responder group (12.10 vs. 10.60 mg/dL, respectively; $P = 0.05$). Otherwise, all other laboratory results including total IgE, antithyroid Abs, Hb level were comparable as illustrated in **Table I**.

And finally, skin prick test results, 14 patients (32.6%) among GFD responder group exhibited positive skin test results for gluten and /or wheat, while 29 (67.4%) patients had negative results. This was significantly higher compared to 6 patients (13%) with positive results in NGS group (p value 0.03).

Discussion

In this study, 49 of 89 patients (55.1%) with CSU showed improvement in urticaria activity following three weeks of a GFD. Of these, 43 patients (48.3% of the total cohort) experienced worsening of symptoms after gluten reintroduction. UAS7 scores decreased significantly during gluten elimination and increased following rechallenge, although they remained below baseline levels. These findings suggest a possible association between dietary gluten exposure and symptom variation in a subset of patients with CSU. However, the uncontrolled study design precludes attributing these changes specifically to gluten elimination or reintroduction.

Our findings are broadly consistent with those of Park et al. (10), who investigated possible gluten sensitivity in patients with urticaria. Nevertheless, evidence supporting gluten elimination in CSU remains limited, and the EAACI/GA²LEN/EuroGuiDerm/APAAACI guideline does not recommend a GFD as a routine therapeutic intervention for CSU (2). Accordingly, the present findings should be considered exploratory and do not establish the efficacy of gluten elimination or justify changes to guideline-based treatment.

Gastrointestinal symptoms were more frequent among GFD responders than nonresponders (58.1% vs. 6.5%). Positive skin prick tests for wheat and/or gluten were also more frequent among responders (32.6% vs. 13.0%). However, these associations do not establish gluten sensitivity or an IgE-mediated mechanism. Although patients with known celiac disease were excluded and celiac serological screening was performed, seronegative celiac disease was not definitively excluded. Furthermore, the higher CRP levels observed in nonresponders require confirmation in larger studies and should not be interpreted as evidence of a distinct inflammatory endotype.

Several limitations should be acknowledged. The absence of a parallel control group, blinding, and a placebo-controlled gluten challenge prevents causal inference and does not exclude spontaneous

fluctuations in CSU activity, placebo or nocebo effects, or responses to other dietary changes accompanying gluten restriction. The short elimination and rechallenge periods limit the assessment of sustained effects, and the exclusion of patients who did not adhere to the diet or were lost to follow-up may introduce selection bias. In addition, the study did not establish a definitive diagnosis of non-celiac gluten sensitivity or completely exclude celiac disease. Larger randomized, blinded, placebo-controlled studies with standardized dietary interventions, comprehensive diagnostic assessment, and longer follow-up are required to determine whether gluten elimination provides a specific clinical benefit in CSU.

In conclusion, gluten elimination was associated with reduced urticaria activity in a subset of patients with CSU, with symptom recurrence following gluten reintroduction. However, the uncontrolled design and short follow-up preclude causal conclusions. Further randomized, placebo-controlled studies are needed before gluten elimination can be recommended as a therapeutic strategy for CSU.

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Author Contributions: STK and EEAK conceived and designed the study. STK, EEAK, and MAE collected clinical data and performed patient recruitment and follow-up. NNN performed/oversaw allergy procedures including skin prick testing and contributed to clinical interpretation. MAA performed the statistical analysis. STK drafted the manuscript. EEAK, MAE, NNN, and MAA critically revised the manuscript. All authors reviewed and approved the final version.

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Table I: General, clinical, and laboratory findings according to gluten sensitivity

	Total (n = 89)	GFD responder (n = 43)	Non-Gluten Sensitivity (n = 46)	P-Value
Age (years)	33.37 ± 10.68	33.88 ± 12.25	32.89 ± 9.08	0.67
Sex				
Male	21 (23.6%)	9 (20.9%)	12 (26.1%)	0.57
Female	68 (75.5%)	34 (79.1%)	34 (73.9%)	
Residency				
Urban	40 (44.9%)	21 (48.8%)	19 (41.3%)	0.48
Rural	49 (55.1%)	22 (51.2%)	27 (58.7%)	
Job				
Housewife	51 (57.3%)	20 (46.5%)	31 (67.4%)	0.16
Office work	13 (14.6%)	8 (18.6%)	5 (10.9%)	
Manual worker	11 (12.4%)	8 (18.6%)	3 (6.5%)	
Student	14 (15.7%)	7 (16.3%)	7 (15.2%)	
Duration (ys) §	4.00 (1.40-7.00)	4.10 (1.50-8.00)	4.00 (1.20-6.00)	0.32
TLC (10 ³ /μL)	6.87 ± 2.10	7.02 ± 1.79	6.73 ± 2.36	0.52
Eosinophils (10 ³ /μL) §	0.10 (0.02-0.27)	0.10 (0.01-0.27)	0.10 (0.03-0.26)	0.33
Basophils (10 ³ /μL) §	0.02 (0.00-0.06)	0.03 (0.00-0.10)	0.01 (0.00-0.04)	0.1
Hb (g/dL)	11.63 ± 1.78	11.57 ± 1.54	11.68 ± 1.98	0.78
CRP (mg/dL) §	11.00 (7.00-15.10)	10.60 (6.00-13.00)	12.10 (7.20-33.30)	0.05*
ESR (mm/hr)	24.37 ± 11.32	24.81 ± 10.97	23.96 ± 11.75	0.72
Total IgE (IU/mL)	100.63 ± 98.19	85.33 ± 65.41	114.93 ± 120.12	0.16
TSH (mIU/L)	2.66 ± 1.56	2.78 ± 1.54	2.54 ± 1.58	0.46
Total IgA (mg/dL)	225.69 ± 103.99	213.39 ± 86.48	237.19 ± 117.84	0.28
Angioedema	42 (47.2%)	24 (55.8%)	18 (39.1%)	0.12
Flatulence and Diarrhea	28 (31.5%)	25 (58.1%)	3 (6.5%)	<0.001*
H. pylori	31 (34.8%)	13 (30.2%)	18 (39.1%)	0.38
Anti-TPO	29 (32.6%)	16 (37.2%)	13 (28.3%)	0.37
AntiThyroglobulin Ab	10 (11.2%)	3 (7.0%)	7 (15.2%)	0.32
ANA	9 (10.1%)	4 (9.3%)	5 (10.9%)	1
Normal Anti-TTG IgA	89 (100.0%)	43 (100%)	46(100%)	-

Data were presented as mean ± SD, §median (IQR), n (%), * Statistically significant p-value between GFD responder and Non-Gluten Sensitivity as p<0.05, TLC:

Total leukocyte count, Hb: Hemoglobin, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, IgE: Immunoglobulin E, TSH: Thyroid-stimulating hormone, IgA: Immunoglobulin A, H. pylori: Helicobacter pylori, Anti-TPO: Anti-thyroid peroxidase, ANA: Antinuclear antibody, Anti-TTG IgA: Anti-tissue transglutaminase immunoglobulin A.

Table II: UAS7 score differences between confirmed and non-gluten sensitivity groups before and after dietary elimination and rechallenging with gluten

	GFD responder (n = 43)	Non-Gluten Sensitivity (n = 46)	p-value
Baseline UAS7 score	33.05 ± 8.95 ^{2,3}	34.09 ± 8.03	0.57
UAS7 score after gluten elimination	14.16 ± 9.72 ^{1,3}	33.02 ± 9.06	<0.001*
UAS7 score after rechallenging with gluten	25.23 ± 8.79 ^{1,2}	33.02 ± 9.06	<0.001*
p-value	<0.001 [§]	0.15	

1 Statistically significant from Baseline UAS in GFD responder group, 2 significant from UAS after gluten elimination in GFD responder group, 3 Statistically significant from UAS after rechallenging with gluten in GFD responder group, UAS: Urticaria Activity Score, *: significant p-value between both groups as p<0.05. § significant p value between UAS in GFD responder group baseline, after elimination and rechallenge.

Figure 1: CONSORT flowchart of the studied patients

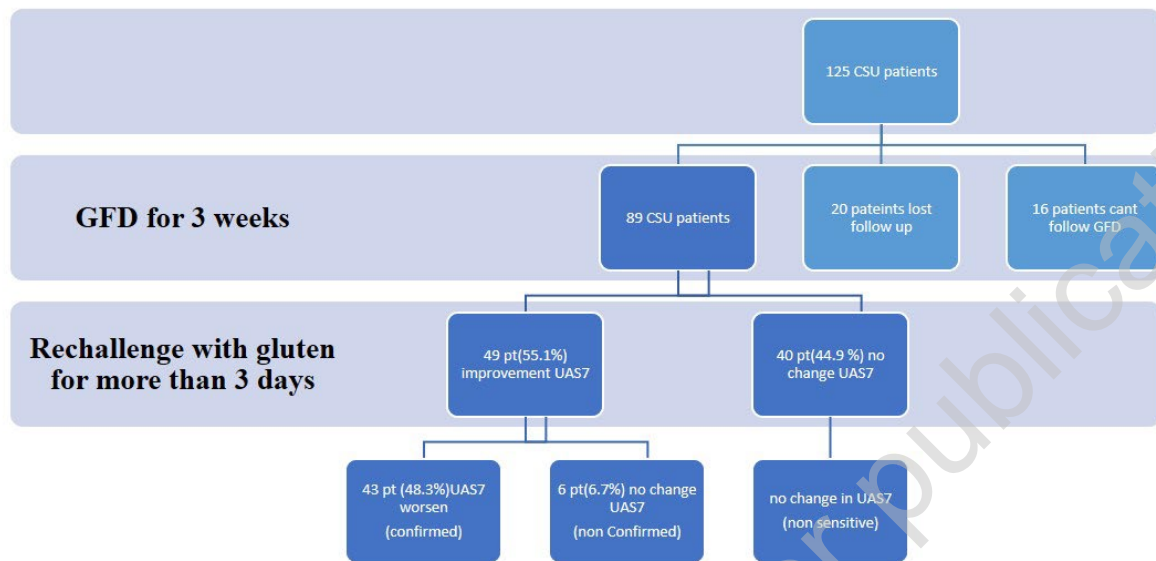


Figure 2: Questionnaire used to assess patient symptoms and dietary adherence (10).

- Disease duration [months]
 - If you prolong the interval between medication doses, do wheals appear?

Score	Wheals	Pruritus
0	None	None
1	Mild (less than 20 wheals/24 hours)	Mild (present but not annoying or troublesome)
2	Moderate (20~50/24 hours)	Moderate (troublesome but does not interfere with normal daily activity or sleep)
3	Intense (more than 50 wheals/24 hours)	Intense (severe pruritus, which is sufficiently troublesome and interferes with normal daily activity or sleep)

- Disease frequency [/week]
 - Name of current urticarial medication(s)
 - Frequency of medication usage

Symptom list	Disease history
Bloating Stomach cramping Headache Joint pain Numbness Chronic fatigue Lactose intolerance	Irritable bowel syndrome Gastritis without ulcers Diabetes Osteopenia or osteoporosis Anemia Thyroid disease Rheumatologic disease Psychologic or neurologic disease Cancer

- Additional drug usage
 - Wheat intake

I eat more than 4 slices of bread per day or the equivalent
I occasionally eat wheat products as a snack
I avoid wheat products
I do not eat wheat products

Figure 3: Change in UAS7 score at baseline and after gluten elimination and rechallenge in both groups (GFD responder, NGS)

