



A Pilot Study about Possible Gluten Sensitivity in Korean Urticaria Patients

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Dear Editor:

Gluten sensitivity (GS) with or without celiac disease (CD) is associated with various dermatologic diseases. Urticaria is a disease that has been reported to improve with a gluten-free diet (GFD), especially if the urticaria is chronic or accompanied with hereditary angioedema¹. Although the incidence of HLA-DQB1*02 (HLA-DQ-2) in the Korean population is less than 5%², non-celiac gluten sensitivity (NCGS) can be present without a genetic predisposition to CD. Furthermore, the prevalence of NCGS in Asia is likely an underestimate due to the relatively lower consumption of wheat compared to Western countries. However, the consumption of wheat products in Korea is rapidly increasing (75 ~ 150 kg/yr)², and studies on NCGS in chronic spontaneous urticarial (CSU) patients in Korea are intriguing. This pilot study was to test the possible existence of NCGS in Korean CSU patients and to develop a screening questionnaire to identify patients who may have NCGS. In addition, we assessed the effect of a GFD on urticarial symptoms in our study patients.

Sixty CSU patients completed this study. Subjects were diagnosed based on CSU criteria according to European Academy of Allergology and Clinical Immunology/Global Allergy and Asthma European Network/European Dermatology Forum/World Allergy Organization guidelines³. To

overcome the weakness of the crossover study design, we only included patients who required medicine and could not endure urticarial symptoms if medications were delayed. The protocol was approved by the Institutional Review Board of the Korea University Guro Hospital (IRB no. 2017GR0267).

A questionnaire was used to collect information about patient concomitant symptoms (Fig. 1). The questionnaire consisted of the following domains: frequency of symptoms, calculated urticarial activity score⁷, medications classified according to strength⁴, presence of gastrointestinal and other symptoms including symptoms related to CD, results of an anti-tissue-transglutaminase IgA test (a sensitive marker for CD)⁵, wheat preference, and the frequency and amount of wheat product intake⁶. The patients were classified into three groups at the end of the study as follows: 'GS possible', 'GS suspected', and 'GS confirmed'. The criteria for each classifying group comprised data from the questionnaire, gluten avoidance period, and the gluten challenge.

During the first week of the GFD, participants maintained their initial dose of urticarial medicine. Patients were then asked to reduce the dose of medication depending on the intensity and frequency of symptoms. All patients kept a diary with daily meals and urticarial activity. Patients who chose not to adhere to the GFD and/or did not want to change their medication were moved to the standard therapy group. After four weeks of observation, the characteristics of the standard therapy group were used as the control (Fig. 2). 'GS possible' status was assigned to patients who were current wheat eaters and had at least one GS-related gastrointestinal symptom or at least three GS symptoms such as bloating, stomach cramping, severe headache, joint pain, numbness, chronic fatigue, and lactose intolerance. On the fourth week of observation, we assessed patient urticarial activity, frequency of medication use, and overall quality of life. Patients who reported symptomatic relief and/or demonstrated a decreased need for urti-

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- 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

Fig. 1. First visit questionnaire. Simplified questionnaire used to collect information regarding concomitant symptoms and to screen for 'gluten sensitivity possible' patients.

carial medicine after four weeks of a GFD were defined as 'GS suspected'. All 'GS suspected' patients were subjected to a gluten challenge the same day that they were defined as 'GS suspected'. For the gluten challenge, patients were instructed to consume 10 g, 20 g, and 30 g of wheat with 100 ml of water twice daily on three consecutive days that equals with 1g of gluten for every 10 g of wheat^{7,8}. Patients recorded urticarial activity and gastrointestinal symptoms for one week, starting on the first day of the gluten challenge. Patients who reported recurrence and/or aggravation of urticarial symptoms during the gluten challenge were defined as 'GS confirmed'.

On the questionnaire, 66% of CSU patients had functional gastrointestinal discomfort. Given the fact that overall prevalence of the irritable bowel syndrome is about 10.1% in South Korea⁹, concomitancy of CU and gastrointestinal discomfort is highly implied. GFD improved both the urti-

caria and gastrointestinal discomfort and gluten challenge aggravated these symptoms of patients. These results support the preexisting theory of relevance between gut inflammation and skin manifestation in gluten-related disorders. And, the pathophysiology of chronic gluten exposure in CSU patients with NCGS should be studied further.

Currently, the maximum allowable amount of gluten for CD patients is 50 mg/d, although there is no established recommendation for NCGS¹⁰. Up until now, the efficacy of a GFD is controversial. However, we found that some patients on the GFD didn't require urticarial medication regularly or they only needed medication at half of their previous dose. Given the natural history of urticaria, this medication reduction is considered significant. In addition, nine patients reported that their quality of life had improved while on the GFD. This is the reason we thought

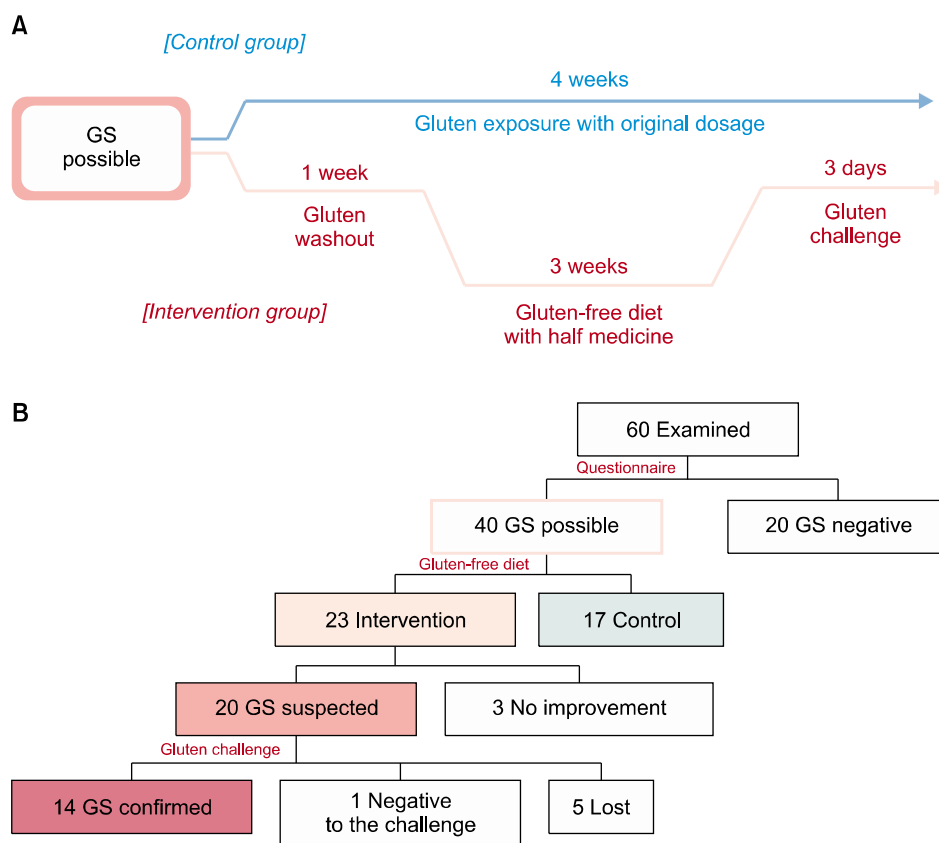


Fig. 2. Flowchart of the study intervention and patients disposition. (A) ‘Gluten sensitivity (GS) possible’ patients maintained their initial dose of medication during the first week of the gluten-free diet while waiting for gluten washout. Patients were then instructed to successively reduce their medication use. Patients who experienced symptomatic relief while on the GFD were labeled as ‘GS suspected’ and were asked to complete a gluten challenge for three days. ‘GS suspected’ patients who developed urticarial symptoms during the challenge were defined as ‘GS confirmed’. (B) Values are presented as the number of patients. Among the 60 screened patients, 40 (‘GS possible’, 66%) had gastrointestinal symptoms. Twenty-three patients agreed to follow a GFD, of which 20 (‘GS suspected’, 87%) experienced an improvement in urticaria symptoms during the 4-week GFD trial. A total of 15 patients then completed the gluten challenge, of which 14 developed urticarial symptoms (‘GS confirmed’, 93%) by the second day of the challenge.

attempting a GFD among patients with suspected NCGS would be worthwhile even though tight adherence to a GFD represents a demanding behavioral modification. The suggested minimum wheat intake to identify GS or CD is four slices of bread per day or its equivalent⁶. However, because most Koreans do not consume that much wheat daily, GS screening criteria based on less wheat intake are needed for Korean. Based on this result, we cautiously suggest consumption of wheat products as occasional snacks as a minimum criterion for diagnosing NCGS. In our study, a GFD was effective for reducing urticarial symptoms in NCGS patients. Specifically, a CSU patient who occasionally consumes wheat product-based snacks and experiences concurrent gastrointestinal symptoms may benefit from a four-week trial of a GFD to confirm NCGS. A pre-clinic questionnaire about gastrointestinal and other symptoms is another potential option to screen for NCGS

in CSU patients.

There were several limitations to the present study. First, it would have been ideal if the consented ‘GS possible’ patients were distributed randomly to the GFD diet. However, a randomized control trial was not feasible given the small sample size of the study. In addition, the Hawthorne effect and placebo effect may have affected our outcome data. To reduce such effects, we conducted the gluten challenge using strict amounts of wheat after the GFD period.

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CONFLICTS OF INTEREST

The authors have nothing to disclose.

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Contribution of Container Types on Cosmetics Contamination

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Dear Editor:

BB cream has surged in popularity worldwide¹. CC cream has also been released, and the BB and CC cushion com-

pact is setting the trend in base makeup. The cushion compact is composed of a urethane puff and a sponge soaked with BB or CC cream that forms a reservoir for the pro-

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