Brief report

Alleviating effect of intranasal zinc on symptoms of allergic rhinitis

Huadong Xu, PhD,[a,b,c]* Keming Tong, BS,[a,b]* Naruhito Iwasaki, MD, PhD,[a,b] Nobutaka Ohgami, PhD,[a,b,d] Akira Tazaki, PhD,[a,b] Takumi Kagawa, MMSc,[a,b] Yanjun Gao, MMSc,[a,b] Delgama A. S. M. Nishadhi, MMSc,[a,b] Akihito Harusato, MD, PhD,[a,b] Masafumi Sakashita, MD, PhD,[e] Kazuhiro Ogi, MD, PhD,[e] Shigeharu Fujieda, MD, PhD,[e] Shogo Sumiya, MD,[a,f] Shinichi Iwasaki, MD, PhD,[f] and Masashi Kato, MD, PhD[a,b] *Nagoya, Toyoake, and Fukui, Japan; and Hangzhou, China*

Background: There is no information about the clinical implications and kinetics of zinc (Zn) in the nasal cavity, a center of allergic inflammation, and serum in subjects with allergic rhinitis (AR).

Objective: Effects of intranasal Zn on symptoms before and after allergen provocation were investigated in humans and mice with or without AR.

Methods: The first clinical follow-up study for Zn levels in nasal epithelial lining fluid (ELF) and serum was conducted in 57 control subjects and 44 patients with Japanese cedar pollinosis (JCP), a representative seasonal AR, from preseason to season. The clinical implications and kinetics of Zn levels in ELF and serum were further investigated in model mice with JCP.

Results: This clinical study showed that the Zn level in nasal ELF from patients with JCP was increased after pollen exposure and became significantly higher than that in nasal ELF from controls in the JCP season. Conversely, the serum Zn level in patients was decreased after pollen exposure and became significantly lower than that in the controls in the JCP season. To further investigate the clinical implication of Zn level, model mice that mimicked the kinetics of intranasal and serum Zn levels as well as the symptoms in patients with JCP were established. The mouse interventional study showed that the symptoms of mice with provocative JCP were significantly improved by treatment with the putative human-equivalent dose of Zn. The relative number of mucin-secreting goblet cells, a sign of provocative allergic rhinitis, in the mice was decreased by intranasal treatment with Zn.

Conclusion: The study's behavioral and pathologic results indicate that an increased level of intranasal Zn can alleviate symptoms of AR. (J Allergy Clin Immunol Global 2025;4:100408.)

Key words: *Allergic rhinitis, zinc, intranasal exposure, Japanese cedar pollinosis, nasal epithelial lining fluid*

Abbreviations used
AR: Allergic rhinitis
Cry j: *Cryptomeria japonica*
ELF: Epithelial lining fluid
JCP: Japanese cedar pollinosis

INTRODUCTION

Japanese cedar pollinosis (JCP) is a typical seasonal allergic rhinitis (AR), an inflammation of the nasal cavity.[1,2] JCP is a large-scale health disturbance induced by Japanese cedar (*Cryptomeria japonica*), including *Cryptomeria japonica* (Cry j) 1 as its representative antigen.[3-5] Considering the global increase in the number of patients with AR, the development of a new therapy to alleviate AR is an urgent task.[3,6,7]

Modulatory effects of various elements on health have been shown in previous studies.[8-12] Cadmium (Cd) and mercury (Hg) are known to be injurious elements that exacerbate immunologic disorders, including AR.[13,14] Because zinc (Zn) is a homologous element for Cd and Hg with similar or opposite properties,[15,16] it may modulate the pathogenesis of AR. Nevertheless, even the level and distribution of Zn in the nasal cavity, a center of inflammation for AR, remain unknown in both animals and humans with AR. Furthermore, there is no information about the effects of nasal Zn level on symptoms of AR.

This study was, to our knowledge, the first prospective follow-up study to compare the Zn levels in the nasal epithelial lining fluid (ELF) and serum in human subjects with and without JCP from the preseason period (January and February) to the JCP season (March and April). The study population consisted of 101 participants (44 patients with JCP and 57 control subjects) (Table I). The clinical implications of

From [a]the Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine; [b]the Voluntary Body for International Healthcare in Universities, Nagoya; [c]the School of Public Health, Hangzhou Medical College; [d]the Department of Hygiene, Fujita Health University, Toyoake; [e]the Division of Otorhinolaryngology-Head and Neck Surgery, Department of Sensory and Locomotor Medicine, University of Fukui; and [f]the Department of Otolaryngology-Head and Neck Surgery, Nagoya City University Graduate School of Medical Sciences.

*These authors equally contributed to this study.

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Corresponding author: Masashi Kato, MD, PhD, Department of Occupational and Environmental Health, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, Aichi 466-8550, Japan. E-mail: kato.masashi.r6@f.mail.nagoya-u.ac.jp.

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TABLE I. Basic characteristics of all participants

Characteristics	Total (N = 101)	Controls (n = 57)	Patients (n = 44)	*P* value
Age (y), mean ± SD	40.76 ± 10.31	41.53 ± 10.34	39.77 ± 10.30	.399*
BMI (kg/m^2), mean ± SD	21.86 ± 3.17	22.04 ± 3.31	21.67 ± 3.00	.602*
Female, no.	56	31	25	.807†
Smoker, no.	31	21	10	.127†
Sleep time (h/d), mean ± SD	6.23 ± 0.93	6.11 ± 0.92	6.39 ± 0.93	.146*
Physical activity (≤2 d/wk), no.	78	45	33	.639†
Japanese cedar pollen–specific IgE (IU/mL), mean ± SD	7.77 ± 14.10	0.12 ± 0.10	11.33 ± 15.89	<.001‡

BMI, Body mass index.
*Student *t* test used for *P* value calculation.
†Chi-square test used for *P* value calculation.
‡Mann-Whitney *U* test used for *P* value calculation.

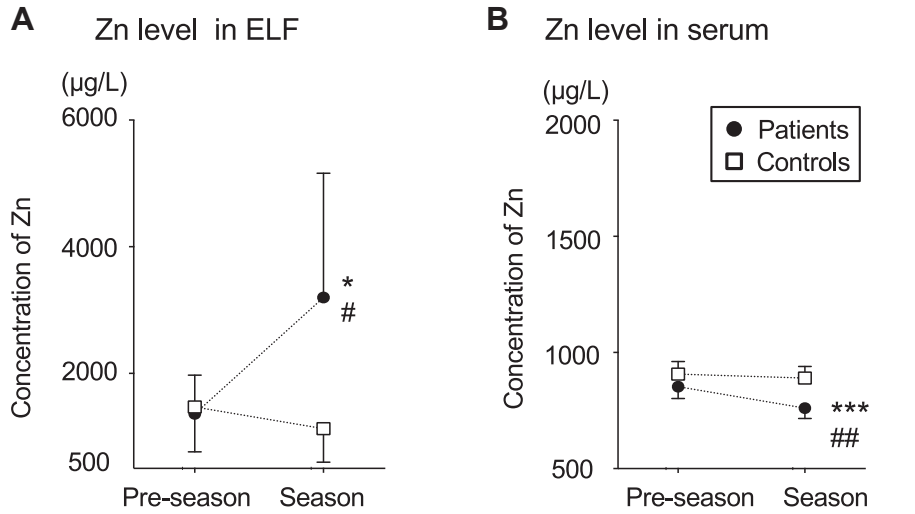

FIG 1. Zn levels in nasal ELF and serum in humans. Zn levels (mean ± 95% CI) in nasal ELF (**A**) and serum (**B**) in the preseason period and the JCP season in controls (Ctrls) and patients with JCP are presented. Significant differences calculated by the Mann-Whitney *U* test (*$P < .05$, ***$P < .001$) or the Wilcoxon test ($^{\#}P < .05$, $^{\#\#}P < .01$).

intranasal Zn level were further elucidated by an interventional study of model mice with JCP.

RESULTS AND DISCUSSION

The Zn levels in the nasal ELF from patients in the JCP season were more than 2.3-fold higher than those during the preseason and more than 2.8-fold higher than the levels in the nasal ELF from the controls in the JCP season (Fig 1 and see Fig E1 in the Online Repository at www.jaci-global.org). In contrast, the Zn levels in serum from patients in the JCP season were significantly (~11%) lower than those in the preseason period and significantly (~15%) lower than those in the serum from the control subjects during the JCP season (Fig 1 and see Fig E1). Our multivariate analysis also established a significant (1.35-fold [95% CI = 0.25-2.45]) increase in Zn levels in nasal ELF and a significant (–0.11 [95% CI = –0.16 to –0.05]) decrease in Zn levels in the serum from the patients (see Fig E2 in the Online Repository at www.jaci-global.org). A previous study showed lower serum Zn levels in patients with provocative AR than in the controls.[17] Another study showed that oral Zn treatment alleviates symptoms of AR accompanied by increased serum Zn levels.[18] The kinetics of Zn in nasal ELF and serum in patients with JCP before and after the natural antigen exposure in this study and those in previous studies suggest a modulatory effect of Zn on the pathogenesis of AR.

It is difficult to demonstrate direct causality between Zn level and symptoms in this human observational study with a relatively small population. Therefore, to clarify the kinetics and clinical role of Zn in JCP, we conducted an interventional study in which mice with and without JCP were exposed to the antigen and/or Zn intranasally. Sensitized mice with allergy that had been sensitized by intraperitoneal injection of Cry j 1 antigen in PBS and unsensitized allergy-free control mice receiving intraperitoneal injection of PBS only were prepared. Then, intranasal challenge with PBS (the control), Zn, Cry j 1 antigen, or Cry j 1 plus Zn was conducted in the mice with allergy and those without allergy (see Fig E3 in the Online Repository at www.jaci-global.org). The frequencies of sneezing (Fig 2, *A*) and nose rubbing (Fig 2, *B*) in the mice with allergy just after intranasal treatment with the antigen (Cry j 1) were 10-fold and 2.3-fold higher than those in the mice without allergy just after intranasal treatment with the solvent (PBS). The relative number of mucin-secreting goblet cells, a pathologic symptom of provocative AR,[3] in the nasal mucosa of the allergic model mice evoked by the antigen was 4.2-fold larger than that in the mice without allergy (Fig 3). These behavioral and

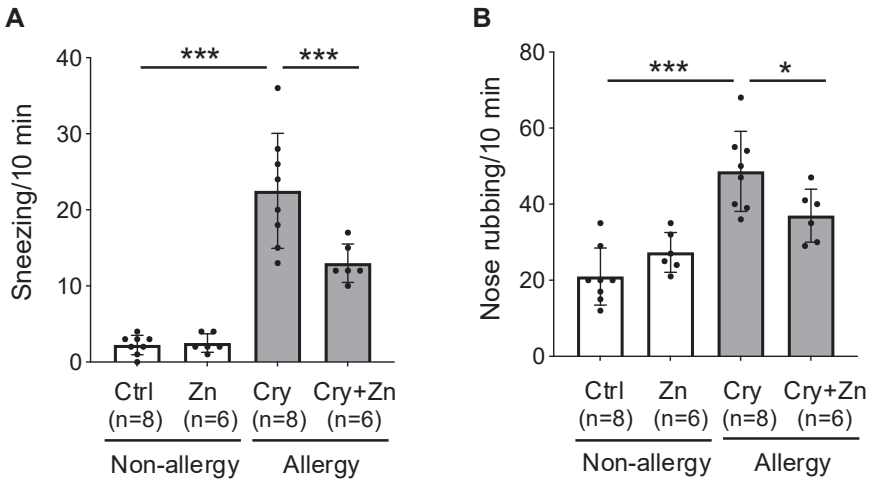

FIG 2. Behavioral analysis. Frequencies (mean ± SD) of sneezing (**A**) and nose rubbing (**B**) for 10 minutes just after the last intranasal challenge with PBS (control [Ctrl]), Zn, Cry j 1 antigen (Cry), or Cry j 1 plus Zn (Cry + Zn) in mice with and without allergy are presented. Individual data points for each mouse are shown as closed circles (**A** and **B**). Significant differences (**P*<.05; ****P*<.001) calculated by ANOVA followed by the least significant difference test.

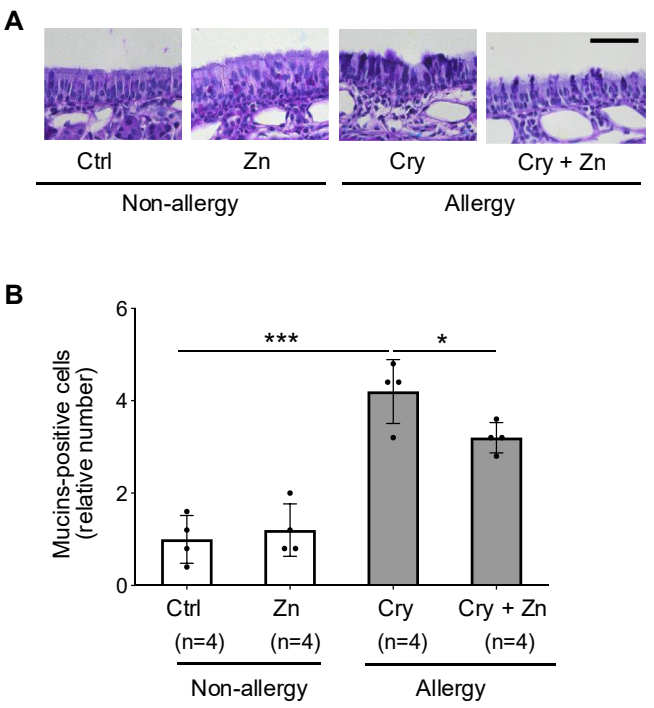

FIG 3. Pathologic analysis. Representative photographs with periodic acid–Schiff staining (**A**) and relative numbers (means ± SDs) of mucin-positive cells (**B**) in nasal mucosa at 24 hours after the last intranasal challenge with PBS (control [Ctrl]), Zn, Cry j 1 antigen (Cry) or Cry j 1 plus Zn (Cry + Zn) in mice with and without allergy are presented. Individual data points for each mouse are shown as closed circles (**B**). Significant differences (**P*<.05; ***P*<.01) calculated by ANOVA followed by the least significant difference test. Bars = 50 μm.

pathologic results indicate the success of establishment of model mice with JCP.

The Zn levels in the nasal ELF (Fig 4, *A*) of the mice with allergy at 24 hours after the last intranasal treatment with the antigen were more than 2-fold higher than those in the nasal ELF of the allergy-free control mice at 24 hours after the last intranasal treatment with its solvent. Conversely, the Zn levels in the serum (Fig 4, *B*) and the relative Zn intensity in the nasal mucosa (Fig 4, *C* and *D*) of the mice with allergyc at 24 hours after the last intranasal treatment with the antigen were about 20% lower and about 24% lower, respectively, than those in the allergy-free control mice at 24 hours after the last intranasal treatment with the solvent. These results indicate similar kinetics of the Zn levels in the nasal ELF and serum between the patients and mice with allergy evoked by the antigen. However, the mechanisms underlying the altered Zn homeostasis in AR remain unclear. A previous study showed an increased level of expression of the Zn efflux transporter ZnT1 in the nasal mucosa of patients with chronic rhinosinusitis.[19] A decreased Zn level in nasal mucosa and an increased Zn level in nasal mucus have also been reported in patients with chronic rhinosinusitis.[20] On the basis of these findings, our results suggest that the leakage of Zn from nasal mucosa to nasal mucus caused by the inflammation-mediated increase in Zn efflux transporter expression results in a decreased serum level of Zn in subjects with allergy. Further studies are needed to investigate the precise mechanisms, including the role of specific Zn efflux transporters and their regulation, with consideration for the different pathogenesis of AR and that of chronic rhinosinusitis.

The effects of intranasal treatment with the putative human-equivalent dose of Zn on symptoms were investigated in the model mice that mimicked the kinetics of Zn levels in nasal ELF and serum as well as symptoms in patients with JCP. The mice with allergy that were treated intranasally with the antigen plus Zn exhibited approximately 42% and 24% lower frequencies of sneezing (Fig 2, *A*) and nose rubbing (Fig 2, *B*), respectively, than those in the mice treated with the antigen alone. These reductions were observed from immediately after intranasal treatment until 10 minutes after treatment. The World Allergy Organization has proposed that a 20% or greater alleviation in immunotherapy for a respiratory allergy is clinically significant.[21] Therefore, the rapid reduction of allergic symptoms induced by the intranasal Zn treatment in the model mice suggests clinical significance of

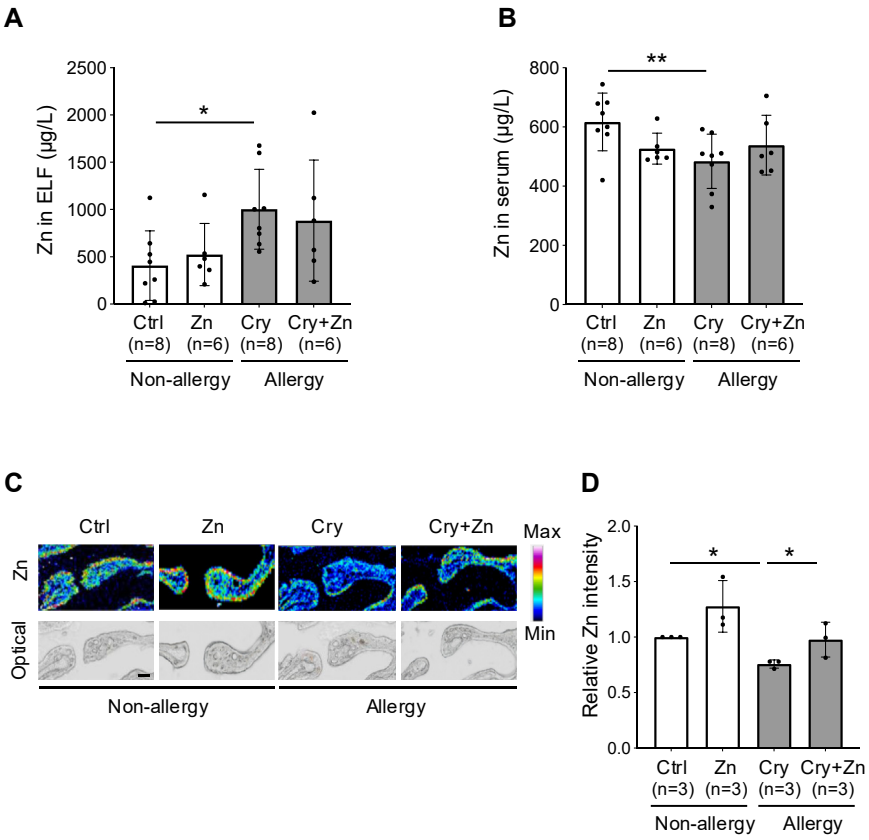

FIG 4. Zn levels in mice. Zn levels in nasal ELF (**A**) and serum (**B**) and representative distributions (**C**) and relative intensities in nasal mucosa (**D**) at 24 hours after the last intranasal challenge with PBS (control [Ctrl]), Zn, Cry j 1 antigen (cry) , or Cry j 1 plus Zn (Cry + Zn) in mice with and without allergy are presented. Individual data points for each mouse are shown as closed circles (**A**, **B**, and **D**). Significant differences (*$P < .05$; **$P < .01$) calculated by ANOVA followed by the least significant difference test. Bars = 100 μm.

intranasal Zn treatment. Furthermore, the relative number of mucin-secreting goblet cells in the nasal mucosa of allergic model mice at 24 hours after the last intranasal treatment with the antigen plus Zn was about 24% smaller than that at 24 hours after the last intranasal treatment with the antigen alone (Fig 3). The relative Zn intensity in the nasal mucosa (Fig 4, *C* and *D*) of the mice with allergy was approximately 30% higher at 24 hours after the last intranasal treatment with the antigen plus Zn than that in control mice with allergy that were treated with the antigen alone. The persistent elevation of Zn levels in nasal mucosa for 24 hours indicates that intranasal Zn treatment has a prolonged effect on local Zn homeostasis. Taken together, these findings from our intranasal intervention study suggest that local Zn treatment alleviates both subjective and objective symptoms of AR.

No clear side effects were detected in this mouse study with intranasal Zn treatment. A previous human study showed no side effects of intranasal Zn treatment at a dose of 44 μg per person.[22] However, intranasal Zn treatment at a higher dose of 1290 μg per person caused nasal irritation and burning.[23] Because this study showed that intranasal Zn treatment at less than 13 μg per person could theoretically alleviate allergic symptoms, further clinical trials are warranted to investigate its efficacy for AR.

In conclusion, this cross-disciplinary approach demonstrated for the first time not only a new clinical implication of intranasal Zn level but also the possibility of intranasal treatment with Zn (nasal drops) as a latent therapy for a global disease (AR).

Data availability statement: The data supporting the findings of this study are available from the corresponding author on reasonable request.

DISCLOSURE STATEMENT

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