Intrinsic atopic dermatitis shows high serum nickel concentration

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Letter to the Editor

Intrinsic atopic dermatitis shows high serum nickel concentration

Dear Editor

Atopic dermatitis (AD) can be divided into two types,[1] serum IgE-high extrinsic AD (EAD), occupying approximately 80% of total AD, and serum IgE-normal intrinsic AD (IAD). We have investigated various clinical and immunological aspects of IAD.[2–5] Female predominate is noted in IAD. While Th2 cells are increased in the peripheral blood of EAD, the frequency of IFN-γ-producing Th1 cells is high in IAD. The mRNA expression of Th1 cytokines, such as interferon (IFN)-γ, in lesional and nonlesional skin from IAD patients are significantly higher than EAD.[6] IAD patients often suffer from metal allergy. Given that protein antigens and metals/haptens give rise to Th2 and Th1 responses, respectively, metals are a candidate of causes for relatively Th1-skewing IAD.

We have previously shown that the frequencies of positive patch tests to nickel, cobalt and chrome in IAD patients are 41.9%, 38.7% and 22.6%, respectively, and 61.3% of IAD patients show positive reactions to at least one of the three metals.[7] This is 2.4-fold higher than that of EAD. A high nickel concentration in sweat of IAD patients was also found.[7] Here, we measured nickel concentration of sera in patients with IAD and EAD, and healthy control (HC). We performed a dietary nickel loading study using a chocolate containing a high nickel dose.

This study was approved by the human medical and ethics committees of both Hamamatsu University School of Medicine and Tohoku University. Patients gave written informed consent. Enrolled in this study were 17 AD patients and 17 HC volunteers. Leukocyte counts, eosinophil percentage, serum IgE, serum specific IgE to *Dermatophagoides pteronyssinus* (DP), serum CCL17/TARC were measured in AD patients. There is no uniform criteria for AD categorization. As previously reported, we classified AD into IAD and EAD by using serum IgE and IgE specific to DP.[7] IAD was defined as serum IgE levels ≤200 kU/L or 200 < IgE ≤ 400 plus class 0 or 1 of IgE specific to *DP* and EAD was defined as 400 < IgE levels or 200 < IgE ≤ 400 plus class 2 or more of the specific IgE. Severity Scoring of AD index (SCORAD) and 100 mm visual analog scale (VAS) for pruritis were used for evaluation of clinical severity of AD. Eight filaggrin gene (*FLG*) mutations common to Japanese AD patients were analyzed as described previously.[2,7]

The nickel loads were applied by using chocolate bar containing a high dose nickel (Lindt chocolate excellence 85% cocoa®, Lindt &Sprungli, Kilchberg, Switzerland). This chocolate contains 470 μg nickel per bar (National consumer affairs center of Japan, 2008). Participants ingested one-half chocolate bar containing 235 μg nickel per day for 4 consecutive days. The dose of 235 μg is nearly equal to the amount of nickel that Japanese eat in daily meal. It was reported that an allergic skin reaction was provoked in individuals sensitive to nickel by 300 μg loading test.[8] Collection of serum samples from peripheral blood were performed before and after nickel loading. Samples were collected 3–6 h after the final ingestion of chocolate. Nickel concentration in serum samples were measured by inductively coupled plasma mass spectrometry (Mitsubishi Chemical Analytec, Tokyo, Japan). All data were expressed as the median and the mean ± standard deviation. Comparisons of serum nickel concentration among the three groups were performed using Kruskall–Wallis test followed by Steel–Dwass's multiple comparisons post hoc test. Statistical significance was ascertained when *P* value was less than 0.05.

The patients' clinical profiles are shown in Table 1. One of male EAD patients claimed to interrupt the subsequent test because of occurrence of palmar dyshidrotic eczema on day 2. One female IAD patient developed facial erythematous lesions on day 3. In these two patients, only the pre-load samples were subjected to nickel measurement. Three of HC agreed to provide only preload serum samples. Total serum IgE levels, SCORAD, and eosinophil percentage were significantly higher in EAD than IAD. There was no significant differences in CCL17/TARC or VAS of pruritus between IAD and EAD. One EAD patient had *FLG* mutation (S2554X) commonly seen in Japanese AD patients.[2]

Fig. 1 shows the nickel concentrations in the sera before (Fig. 1A) and after nickel loading (Fig. 1B). The nickel concentration levels (mean ± SD, ng/ml) before loading test were 2.79 ± 1.90 (IAD), 1.43 ± 2.15 (EAD), and 0.40 ± 0.93 (HC), respectively (median: 2.68, 0.41, and 0.00). The IAD patients had significantly higher nickel levels than did the HC subjects (Fig. 1A). The nickel concentration levels were 1.82 ± 2.12 and 0.40 ± 0.93 in AD and HC, respectively ($P = 0.02$). There was no strong correlation between the nickel concentration and SCORAD, but a weak correlation was observed in EAD ($R = 0.52$, $P = 0.08$). After nickel loading, the mean nickel levels were 3.59 ± 0.47 (IAD), 2.05 ± 2.87 (EAD), and 0 ± 0 (HC), respectively, (median: 3.83, 0.67, and 0.00). Thus, the high serum nickel concentration in IAD became more discernible as compared with EAD and HC (Fig. 1B). However, significant nickel increment was not found in the post-loading data, although a minimal increase was detectable in the IAD patients.

Our study clearly demonstrated that the serum nickel concentration is constitutionally high in IAD patients compared with EAD and HC individuals. Notably, the nickel concentration was 7.0-fold higher in IAD than HC before nickel loading. Even the nickel patch test-negative IAD patients had high serum nickel levels, suggesting that systemic metal allergy might occur in non-skin

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Table 1
Subject characteristics.

	Intrinsic AD	Extrinsic AD	Healthy controls	P value*
Patients	5 (1 men and 4 women)	12 (10 men and 2 women)	17 (5 men and 12 women)	
Age (years, mean ± SD)	39.2 ± 5.9	35.9 ± 11.3	22.6 ± 5.0	0.45
Sex (male: female, %)	20.0%: 80.0%	83.3%: 16.7%	29.4%: 70.6%	0.03
IgE (kU L^{-1}, mean ± SD)	57.4 ± 50.9 (n = 5)	9080.3 ± 10803.1 (n = 12)	N.A.	0.01
CCL17/TARC (pg mL^{-1}, mean ± SD)	849.3 ± 1047.4 (n = 4)	2161.3 ± 1521.4 (n = 12)	N.A.	0.09
Eoshinophil (%, mean ± SD)	2.6 ± 1.3 (n = 5)	11.9 ± 6.9 (n = 12)	N.A.	<0.01
SCORAD (mean ± SD)	35.5 ± 17.1 (n = 5)	61.0 ± 15.0 (n = 12)	N.A.	0.02
VAS of pruritis (mean ± SD)	44.2 ± 28.9 (n = 5)	70.0 ± 16.4 (n = 12)	N.A.	0.12
FLGmutation (%)	0 (n = 4)	1 (n = 7)	N.A.	1

*Wilcoxon rank sum test or Fisher's exact test applied for IAD vs EAD.
N.A., no assessment.

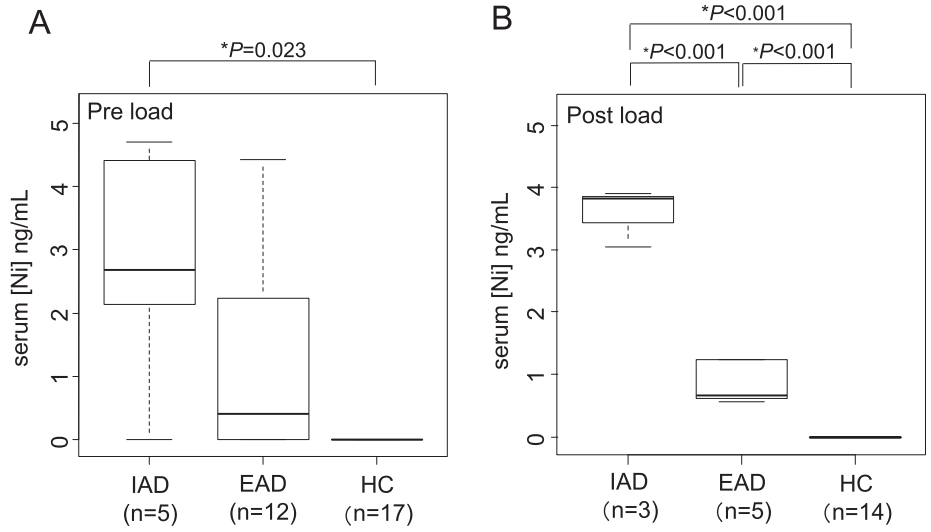

Fig. 1. Box plot of the nickel concentration in serum before/after provocation test in the three groups (IAD, EAD, and HC). Serum samples were obtained before (A, preload) and after (B, postload) nickel loading. When a significant difference was observed in the Kruskal–Wallis test, Steel–Dwass multiple comparison post hoc test was performed. Indicated with an asterisk (*) ($P < 0.05$) is statistically significant difference. The rectangle spans the first quartile to the third quartile. A segment inside the rectangle shows the median, and whiskers above and below the box show the locations of the minimum and maximum. Longest length of the whisker is up to 1.5 times of the length of the box.

sensitized patients. Nickel and cobalt have the ability to induce allergic reactions by directly stimulating toll-like receptor 4 on antigen presenting cells.[9,10] Therefore, our finding suggests that serum nickel sensitize circulating T cells and they express skin-homing receptors upon repeated elicitation with serum nickel and migrate to the lesional skin.

Although the post-loading data more clearly showed the high level of nickel concentration in IAD, the dietary nickel loading did not effectively increase the nickel concentration. Thus, the twice excess intake of metal-containing foods does not substantially increase the metal concentration in sera. Our finding provides an implication that the absorption or transport of nickel in IAD patients is abnormally upregulated in a steady state.

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Conflict of interest
The authors have no conflict of interest to declare.

Hayato Yamaguchi [a,*], Noriyasu Hirasawa [b], Sanki Asakawa [b], Kiyuki Okita [b], Yoshiki Tokura [a]

[a] *Department of Dermatology, Hamamatsu University School of Medicine, Shizuoka, Japan*
[b] *Laboratory of Pharmacotherapy of Life-Style Related Diseases, Graduate School of Pharmaceutical Sciences, Tohoku University, Miyagi, Japan*

* Corresponding author. Department of Dermatology, Hamamatsu University School of Medicine, 1-20-1 Handayama, Higashi-ku, Hamamatsu, Shizuoka 431-3192, Japan.
E-mail address: yamaguchihaya@gmail.com (H. Yamaguchi).

References

1. Kabashima K. New concept of the pathogenesis of atopic dermatitis: interplay among the barrier, allergy, and pruritis as trinity. *J Dermatol Sci* 2013;**70**:3–11.
2. Kabashima-Kubo R, Nakamura M, Sakabe J, Sugita K, Hino R, Mori T, et al. A group of atopic dermatitis without IgE elevation or barrier impairment shows a high Th1 frequency: possible immunological state of the intrinsic type. *J Dermatol Sci* 2012;**67**:37–43.
3. Yamaguchi H, Hata M, Fujiyama T, Ito T, Hashizume H, Tokura Y. Psychological aspects of patients with intrinsic atopic dermatitis. *Eur J Dermatol* 2014;**24**:253–4.
4. Tokura Y. Extrinsic and intrinsic types of atopic dermatitis. *J Dermatol Sci* 2010;**58**:1–7.
5. Mori T, Ishida K, Mukumoto S, Yamada Y, Imokawa G, Kabashima K, et al. Comparison of skin barrier function and sensory nerve electric current perception threshold between IgE-high extrinsic and IgE-normal intrinsic types of atopic dermatitis. *Br J Dermatol* 2010;**162**:83–90.

6. Suárez-Fariñas M, Dhingra N, Gittler J, Shemer A, Cardinale I, de Guzman Strong C, et al. Intrinsic atopic dermatitis shows similar TH2 and higher TH17 immune activation compared with extrinsic atopic dermatitis. *J Allergy Clin Immunol* 2013;**132**:361–70.
7. Yamaguchi H, Kabashima-Kubo R, Bito T, Sakabe JI, Shimauchi T, Ito T, et al. High frequencies of positive nickel/cobalt patch tests and high sweat nickel concentration in patients with intrinsic atopic dermatitis. *J Dermatol Sci* 2013;**72**:240–5.
8. Jensen CS, Menné T, Lisby S, Kristiansen J, Veien NK. Experimental systemic contact dermatitis from nickel: a dose-response study. *Contact Dermat* 2003;**49**:124–32.
9. Raghavan B, Martin SF, Esser PR, Goebeler M, Schmidt M. Metal allergens nickel and cobalt facilitate TLR4 homodimerization independently of MD2. *EMBO Reports* 2012;**13**:1109–15.
10. Schmidt M, Raghavan B, Müller V, Vogl T, Fejer G, Tchaptchet S, et al. Crucial role for human Toll-like receptor 4 in the development of contact allergy to nickel. *Nat Immunol* 2010;**11**:814–9.

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