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Dietary Intervention for Control of Clinical Symptom in Patients with Systemic Metal Allergy: A Single Center Randomized Controlled Clinical Study

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Patients with eczema with a systemic metal allergy, such as nickel (Ni), cobalt (Co), chromium (Cr), and tin (Sn), should pay attention to symptomatic exacerbation by excessive metal intake in food. However, dietary intervention for systemic metal allergy can be difficult. In this study, we evaluated the effect of dietary intervention by a registered dietitian on clinical symptoms in patients with a systemic metal allergy. Forty-four patients with cutaneous symptoms who were diagnosed with a metal allergy were randomly assigned to the dietary intervention group (DI group, n = 29) by a registered dietitian or the control group (C group, n = 15). The DI group was individually instructed by a registered dietitian how to implement a metal-restricted diet and then evaluated 1 month later. Dermatologists treated skin lesions of patients in both groups. Skin symptoms assessed by the Severity Scoring of Atopic Dermatitis (SCORAD) index, blood tests, and urinary metal excretion were evaluated. The DI group showed decreased Ni, Co, Cr, and Sn intake (all $P \leq 0.05$), and an improved total SCORAD score, eczema area, erythema, edema/papulation, oozing/crust, excoriation, lichenization and dryness after 1 month of intervention compared with before the intervention (all $P \leq 0.05$). However, the C group showed decreased Ni and Sn intake and an improved oozing/crust score (all $P < 0.05$). It showed the effective reduction of dietary metal intake controls dermatitis due to a metal allergy. In conclusion, dietary intervention by a registered dietitian is effective in improving skin symptoms with a reduction in metal intake.

INTRODUCTION

The Guideline for the Management of Contact Dermatitis was issued by the Contact Dermatitis Guideline Committee of the Japanese Dermatological Association. This guideline states that, after the formation of contact sensitization through contact, when the same antigen enters an organism through a non-percutaneous route (e.g., orally, through inhalation, or injection), dermatitis may occur over the whole body. When the cause of dermatitis

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is a metal, this is commonly known as a systemic metal allergy (1, 2). A previous study showed that, among 1,929 cases of metal allergens in the Japanese standard allergen patch test in 2014, metal allergens with a high positive rate were nickel (Ni) sulfate (24.8%), cobalt (Co) chloride (7.9%), and potassium dichromate (2.3%) (2). Positive rates for many metals have been increasing since 2010 (2).

In the treatment of any metal allergy over the whole body, avoiding related antigens, including transcutaneous contact, is necessary. If the symptoms do not show any improvement, a restriction of metal intake should be considered for the dietary intake of the patient. The ingestion of trace elements in the diet and corresponding metal intake through mucous membranes of the oral cavity or digestive organs can lead to various types of dermatitis in patients with whole-body metal allergies (3–5). A restriction of this intake decreases the severity of the symptoms in systemic metal allergy. However, a strict metal restriction diet results in a deficiency of trace elements, and this should be avoided. Therefore, if a 1-month metal-restricted diet does not show any effect, that diet should be discontinued (6).

The metal intake level in Japan for Ni is 110–175 μg/day, Co is 7–10 μg/day, chromium (Cr) is 15–34 μg/day, and tin (Sn) is <100 μg/day (7). Regarding dietary treatment for patients with a Ni allergy, one report showed that any symptom occurred depending on the intake level of Ni (8). Furthermore, an experimental oral load of 300 μg/day of Ni showed a tendency for aggravation of the skin condition (8). A case report showed that a patient on a diet of 300 μg/day of Ni showed improvement when a metal-restricted diet of 100 μg/day of Ni was applied (9). There have been no reports of results for Co, Cr, or Sn in Japan. However, Co and Cr levels have been reported in the USA (10) and India (11). Urinary Ni excretion is decreased after 10 days fasting (12). However, increased urinary Ni excretion has been reported with dietary supplementation and consumption of Ni-rich food (13).

In most cases, dietary guidance for patients with a metal allergy is simply provided by the doctor at the time of the consultation. Calculation of the amount of nutrients including metals in the patient's diet before and after dietary guidance has not been reported, and the importance of dietary intervention has not been clarified.

This study was conducted to test the following hypotheses: patients with metal allergies have a diet with a high degree of metal intake, dietary intervention by a registered dietician can reduce the intake of metals, a reduction in the metal intake can improve allergy symptoms, and a reduction in urinary metal excretion is expected following the restriction of dietary metals.

MATERIALS AND METHODS

Participants

This study included 44 adult patients with various types of eczema, such as atopic dermatitis, nummular eczema, prurigo, pompholyx, and hand eczema, at Kobe University Hospital with 934 beds. After taking patch tests, these patients were diagnosed as being allergic to one or more of the following metals: Ni, Co, Cr, and Sn. However, children younger than 15 years or patients who were already on a diet were excluded. This study was conducted from June 2015 to May 2018. We completed the study as we had the planned number of patients.

Methods

This study was a two-arm, randomized, controlled clinical study (Figure 1). This study was approved by the Ethics Committee of Kobe University School of Health Sciences (permission No: 295, approved in July 2014) and registered with the University Hospital Medical Information Network (No: UMIN000017499). All participants were included in this study after providing their informed consent and randomized by envelope. The 30 cards for the dietary intervention (DI) group and 15 cards for the control (C) group were placed in an envelope in advance, and the patient took the cards. The doctor confirmed it, and the doctor kept the assignment by the card. A group of 30 patients participated in a nutritional intervention program conducted by registered dietitians (dietary intervention [DI] group). We also included a randomly selected control group of 15 patients who did not participate in the intervention program. The number of cases could not be ascertained due to the lack of previous studies, and the number of cases was limited at a single hospital. Then, the number of participants was set to be 10 each in the good or poor adherence DI groups and the C group, taking into account the possibility of dropouts. In the DI group, one of 30 patients signed a prior informed consent form but did not participate in the first intervention. Therefore, we conducted data analysis on 29 patients. All evaluations were conducted one month after the start of study. The primary endpoint was changes of the Severity Scoring of Atopic Dermatitis (SCORAD) score and the secondary endpoints were dietary intake and metal intake changes. The data obtained in the study were stored with the strictest security by the Department of Nutrition at Kobe University Hospital, and the greatest care was taken to prevent any data leakage.

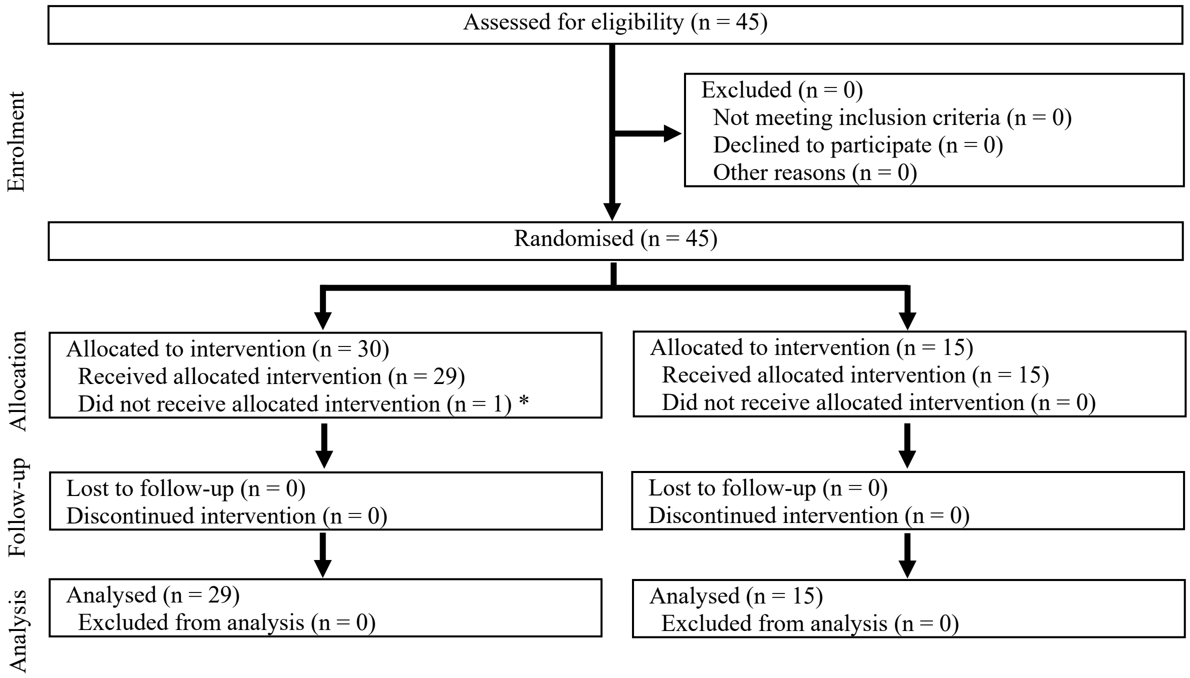

Figure 1. Flow diagram of the progress through the phases of a parallel randomized trial of 2 groups (that is, enrollment, intervention allocation, follow-up, and data analysis).
*The patient stopped coming to see the doctor after the day of the allocation.

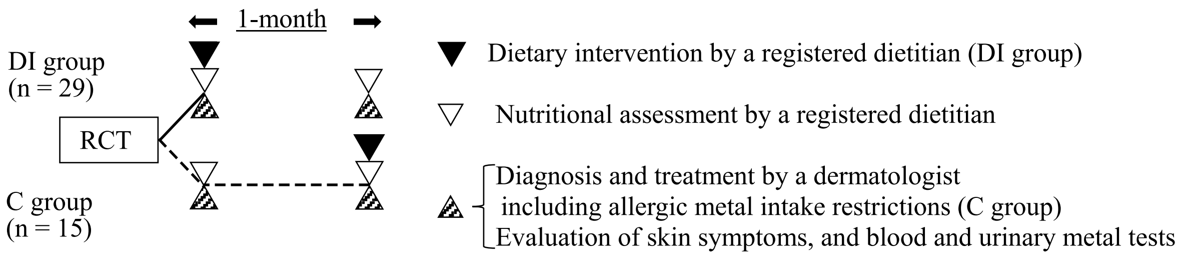

Figure 2. Study design.
The study was a two-arm, randomized, controlled, clinical trial. The solid line indicates the process by a dietitian in the DI group and the dotted line indicates the process by a dermatologist.
DI, dietary intervention; C, control; RCT, randomized, controlled trial.

Dietary intake survey

Patients recorded their food intake for 3 days immediately before the start and end of the program, and the registered dietitian checked the details of the meal records and calculated the nutritional amounts. Furthermore, we calculated nutritional metal intake using the Japanese Windows software Excel Eiyo-kun Ver. 6.01 (Kenpakusha; Tokyo, Japan) which includes the standard tables of food composition in Japan (14), and we added data from the trace element food composition table (15).

Nutritional guidance

The duration of the nutritional intervention program was 1 month (6) (Figure 2). We used a commonly used nutrient requirement program and a specific metal restriction program for the dietary intervention [Appendix 1 (16, 17), 2 (15), and 3]. Dermatologists instructed both groups on the first day of the intervention using the food list shown in Appendix 1 and 2. In the DI group, a registered dietitian provided guidance for all these materials on the first day of the intervention. However, patients in the C group received the same intervention as the DI group on the last day after the study ended for ethical reasons. All dietary records were checked and evaluated by the registered dietitian.

Required nutritional level

The required nutritional level was prepared by the Kobe University Hospital Department of Nutritional to ensure that the study participants had the necessary nutritional levels (Appendix 3). The required nutritional level was calculated on the basis of the Dietary Reference Intakes for Japanese (2015 edition) (18) released by the

Formulation Review Committee of the Minister of Health, Labour and Welfare with reference to age, sex, and body indices (body mass index: BMI). The activity level was calculated using a formula in the Food Frequency Questionnaire based on food groups (FFQg Ver. 3.5) (19). When the BMI was <25 kg/m2, the required energy level (kcal/day) = standard basal energy expenditure value (kcal/kg weight/day) × the standard weight (ideal body weight: IBW) × the body activity level. When the BMI was 25–29.9 kg/m2, the required energy level (kcal/day) = [0.0481 × weight (kg) + 0.0234 × height (cm) − 0.0138 × age (years) − a fixed constant (men: 0.4235, women: 0.9708)] × 1,000/4.186 × the body activity level. When the BMI was ≥30 kg/m2, the required energy level (kcal/day) = IBW (kg) × 25 − 30 (kcal) (20). However, if low-density lipoprotein-cholesterol and triglyceride concentrations were high in blood tests, the registered dietician advised the patients to improve their diet (21).

Metal restrictions

In this study, patients who were positive for Ni, Co, Cr, or Sn in the patch test were provided a restricted diet. Dermatologists used the conventional list of metal-rich foods and provided patients with the same instructions (Appendix 1 and 2). Furthermore, at the start of the program, a registered dietitian individually instructed the DI group how to implement a metal-restricted diet to address the dietary habits on dietary records of each patient with a detailed dietary intervention (7).

Evaluation of the clinical symptoms by dermatologists

On the day that the nutritional intervention program was started and on the last day of the program, we used Japanese revised version of SCORAD index (23) developed originally by the European Task Force on Atopic Dermatitis (Appendix 4) (24). The severity was evaluated in the SCORAD system as follows: A, extent of skin eruption (%); B, diversity (6 items), such as erythema and edema/papulation (swelling), oozing/crust, excoriation, lichenization, and dryness, and the strength of the symptoms (0–3 points per item); and C, subjective symptoms (itching sensation: 0–10 points, sleep disturbance, somnipathy: 0–10 points) expressed as a number (sum total [points] = A/5 + 7B/2 + C, with a top score of 103 points). An itching sensation and pain were evaluated using a visual analog scale.

Blood tests

Laboratory data, such as biomarkers associated with atopic dermatitis (e.g., non-specific immunoglobulin E [IgE], lactate dehydrogenase, eosinophils, and thymus and activation-regulated chemokine) were measured in the Kobe University Hospital Laboratory Medicine.

Urine analysis

Quantitative analysis of metals in urine was outsourced to the Testing and Analysis Division at Shimadzu Techno-Research, Inc., (Kyoto, Japan). A volume of 0.5 ml of a urine sample and 0.4 ml of nitric acid (1 + 1) were added to a sealed container, and microwave decomposition was conducted (180°C for 5 min). After cooling down, the volume was increased to 10 ml with pure water to create the measurement solution. This solution underwent inductively coupled plasma mass spectrometry, and Ni, Co, Cr, and Sn were quantified. The limit of detection for each metal was as follows: Cr, 0.48 ng/ml; Co, 0.24 ng/ml; Ni, 0.80 ng/ml; and Sn, 0.35 ng/ml. Urine creatinine concentrations were measured in the Kobe University Hospital Laboratory Medicine, and the metal concentration to creatinine ratio was calculated.

Table I. Background of the patients

		DI group (n = 29)		C group (n = 15)	
		Before intervention	After intervention	Before intervention	After intervention
Males/females		14/15		3/12	
Age	(y)	52.1 ± 18.2		48.8 ± 17.5	
Height	(cm)	161.3 ± 6.4		159.5 ± 4.2	
IBW	(kg)	57.4 ± 4.6		56.0 ± 2.9	
Weight	(kg)	62.7 ± 13.1	62.3 ± 13.1	59.8 ± 9.8	59.7 ± 9.7
BMI	(kg/m^2)	24.0 ± 4.3	23.8 ± 4.2	23.5 ± 3.8	23.5 ± 3.8

Values are numbers or the mean ± standard deviation. No significant differences were observed in the dietary intervention and controls groups between before and after the intervention. DI, dietary intervention; C, control; IBW, ideal body weight. IBW = height (m^2) × 22. BMI, body mass index. BMI = body weight (kg) ÷ height (m^2).

Table II. Positive patch test results and the change in SCORAD scores

Group	Case	Patch test results				SCORAD score	
		Ni	Co	Cr	Sn	Before intervention	After intervention
DI	1	+	+	+	+	9.2	4.7
	2	+	+	+	−	55.6	45.0
	3	+	+	+	−	46.0	28.3
	4	+	+	+	−	10.8	3.5
	5	+	+	+	−	5.9	7.2
	6	+	+	−	+	39.0	35.0
	7	+	+	−	−	19.4	15.2
	8	+	−	+	+	48.4	33.5
	9	+	−	+	−	54.0	31.9
	10	+	−	+	−	53.1	43.8
	11	+	−	+	−	35.7	18.0
	12	+	−	−	+	51.0	41.6
	13	+	−	−	+	48.0	37.5
	14	+	−	−	−	25.7	16.5
	15	−	+	−	−	63.5	70.0
	16	−	+	−	−	63.0	52.0
	17	−	+	−	−	57.8	36.4
	18	−	+	−	−	33.8	25.0
	19	−	+	−	−	20.9	11.0
	20	−	−	+	+	45.0	27.4
	21	−	−	+	+	39.1	14.1
	22	−	−	+	+	34.0	16.4
	23	−	−	+	−	55.0	45.0
	24	−	−	+	−	47.0	22.8
	25	−	−	+	−	38.2	39.5
	26	−	−	−	+	65.3	47.4
	27	−	−	−	+	33.7	28.3
	28	−	−	−	+	27.5	27.3
	29	−	−	−	+	26.8	25.0
C	1	+	+	−	−	10.7	11.6
	2	+	−	−	−	61.5	32.4
	3	+	−	−	−	59.3	66.5
	4	+	−	−	−	52.8	32.1
	5	+	−	−	−	49.1	38.5
	6	+	−	−	−	43.1	39.6
	7	+	−	−	−	28.5	31.7
	8	−	+	+	−	41.0	42.9
	9	−	+	−	+	40.7	33.7
	10	−	+	−	−	57.0	51.9
	11	−	+	−	−	14.5	7.1
	12	−	−	+	−	27.7	30.6
	13	−	−	−	+	44.3	38.3
	14	−	−	−	+	40.0	43.0
	15	−	−	−	+	10.4	14.5

The patch test results were positive (+) or negative (−). The total SCORAD scores before and after treatment are shown. SCORAD, Severity Scoring of Atopic Dermatitis; DI, dietary intervention; C, control; Ni, nickel; Co, cobalt; Cr, chromium; Sn, tin.

Statistical analyses

Statistical analysis was conducted using IBM SPSS Statistics, Version 23 (IBM Corp.; Tokyo, Japan). We used the chi-square test, paired sample t-test, Wilcoxon signed-rank test, Student’s t-test, and Mann-Whitney U-test for comparison between groups. Values of $p < 0.05$ were considered to be significant.

RESULTS

Participants' characteristics and nutritional intake

Forty-five patients were randomly allocated, but one patient in the DI group did not participate in the intervention. There were no significant differences in the patients' background before the study between the DI and control groups (Table I). Among the 44 patients in this study, 21, 17, 17, and 16 were allergic to Ni, Co, Cr, and Sn, respectively (Table II). Specifically, in Ni-allergic patients, the total SCORAD score improved by 92.9% in the DI group and by 57.1% in the C group after the dietary intervention compared with before the dietary intervention (Table II). The BMI in both groups was <25 kg/m^2 and well within the target range for an appropriate BMI (18). Regarding nutritional intake, the ratio of the actual energy intake to the energy requirement in the DI group showed 15% excess before the intervention. However, after the intervention, this ratio was decreased ($p < 0.01$) and showed an improvement to an appropriate level (Table III). The C group showed a 10% excess energy intake before the intervention and no significant improvement after the intervention. The protein energy ratio ranged between 13% and 20%, the lipid energy ratio ranged between 20% and 30%, and the carbohydrate energy ratio ranged between 50% and 65% in the DI and control groups after the study. Both groups were within the range of the recommended intake levels (18), and no significant differences in these ratios were observed before and after the intervention between the two groups.

In the DI group, the intake of Ni, Co, Cr, and Sn was decreased after the intervention compared with before the intervention (all $p < 0.01$). However, in the C group, only the intake of Ni and Sn were decreased after the intervention compared with before the intervention (all $p < 0.05$) (Table III). Because the energy intake was decreased, we analyzed the change in the amount of metal intake in relation to the energy intake considering the importance of their balance to avoid iatrogenic malnutrition. The Ni intake/energy intake ratio was decreased after the intervention compared with before the intervention in both groups ($p < 0.01$ in the DI group and $p < 0.05$ in the C group). The Co intake/energy intake ratio was decreased after the dietary intervention compared with before the dietary intervention in the DI group ($p < 0.01$).

Skin symptoms

A decrease in the eczema area, erythema, edema/papulation, oozing/crust, excoriation, lichenization, dryness, total SCORAD (B) score, and total SCORAD scores was observed after the dietary intervention compared with before the dietary intervention in the DI group (all $p < 0.05$) (Figure 3). However, only the oozing/crust score was improved after the intervention in the C group ($p < 0.05$). The rate of improvement in the total SCORAD score was 92.9% and 57.1% in Ni-positive patients, 83.3% and 60.0% in Co-positive patients, 86.7% and 0.0% in Cr-positive patients, and 100.0% and 50.0% in Sn-positive patients in the DI and control groups, respectively (Cr, Sn: both $p < 0.01$; Ni: $p < 0.05$). Visual analog scale scores for itching and pain did not change after the intervention.

Blood tests

Nutritional abnormalities, such as metabolic syndrome and malnutrition (undernutrition), were not observed in either group (Table IV). Some significant differences in white blood cells, platelet counts, aspartate aminotransferase, γ-glutamyl transferase and low-density lipoprotein cholesterol values were observed between before and after sampling, but they were within the normal range. TARC concentrations in both groups were mildly elevated. There was no significant improvement in Th2 inflammation-related biomarkers, such as eosinophils and non-specific IgE.

Metal in urine

The mean (± SD) urinary Ni concentration in the DI group appeared to be decreased after the dietary intervention compared with before the dietary intervention (1.798 ± 2.841 µg/g creatinine and 0.804 ± 1.124 µg/g creatinine, before and after the intervention, respectively), but this was not significant. However, the mean Ni concentration in the C group was not different between before and after the intervention (1.821 ± 2.537 µg/g creatinine and 1.843 ± 2.892 µg/g creatinine, before and after the intervention, respectively). Other metal concentrations varied widely and did not change between before and after the intervention.

DISCUSSION

The primary aim of the present study was to evaluate the effect of therapeutic dietary intervention by a registered dietitian on patients with systemic metal allergy compared with those who only had instructions provided by a dermatologist. The DI group showed improved skin eruptions, as shown by an improvement in eczema, erythema, edema/papulation, oozing/crust, excoriation, lichenization, dryness, the total SCORAD (B) score, and the total SCORAD score. However, only oozing/crust was improved in the C group. A higher dietary metal intake of Ni, Cr, and Sn in the enrolled patients with a systemic metal allergy than the general intake level in Japan was indicated by a registered dietitian's assessment (8). The DI group showed decreased Ni, Co, Cr, and Sn intake, but only Ni and Sn intake were decreased in the C group after the intervention. Urinary metal measurement showed no change and did not match the metal intake results. Regarding nutritional intake balance, energy intake in the DI group was <15% over the Japanese dietary reference intake (14) and decreased after the study. Energy intake in the C group showed an excess of 10% and was not decreased after the intervention. The Ni and Co intake/energy intake ratios were decreased in the DI group, and the Ni intake/energy intake ratio was decreased in the C group after the intervention compared with before the intervention.

The effectiveness of the dietary intervention was the main outcome in this randomized, controlled study. Our results supported the hypothesis that a dietary intervention by a registered dietitian is effective for reducing dietary metal intake and improving dermatitis symptoms in systemic metal allergy. In this study, dermatologists provided simple uniform instructions to all patients and data in the C group show their results. Patients in the C group showed an improvement rate of 51.7% in those with a Ni allergy, which is comparable to that described in Veien's review (1), which indicated the effectiveness of decreasing Ni intake in half of their patients. In contrast, patients with a Ni allergy in the DI group showed an improvement rate of 92.9%. The DI group showed significantly improved skin clinical symptoms, but showed no significant changes in Th2 inflammation related-biomarkers, such as non-specific IgE, eosinophils, and Thymus and Activation-Regulated Chemokine. The predominant eczema subtype in this study was atopic dermatitis. Atopic dermatitis can be divided into extrinsic atopic dermatitis and intrinsic atopic dermatitis on the basis of serum IgE concentrations. The frequency of interferon-γ-producing Th1 cells is high, and metal allergy is a candidate of causes for relative Th1 skewing in intrinsic atopic dermatitis (25). Therefore, patients with atopic dermatitis and a metal allergy who were enrolled in this study may be similar to those with intrinsic atopic dermatitis. We assume that there was no change in Th2-related biomarkers because patients in whom Th1 was strongly involved in the formation of the pathology were enrolled in this study.

A registered dietitian consulted with each patient and checked the diet record of patients in both groups for 3 days using the materials shown in Appendix 3 before the intervention. Moreover, on the first day of the intervention, each patient in the DI group was individually given specific instructions regarding nutritional needs and metal restrictions by a registered dietitian. By the intervention, patients could understand their own eating habits and correct their eating habits. Our study clearly indicated a decrease in intake of all four metals in the DI group as a result of maintaining a suitable dietary habit for 1 month. Nutritional guidance for 30 minutes was performed in this study as a research process. Thirty minutes of guidance is used by national insurance system in Japan for common diseases, such as cancer, diabetic mellitus, and cardiovascular disease. But systemic metal allergies are not covered yet. Only food allergies in children younger than 9 years are applied in allergic disease.

Table III. Metal and nutritional intake

		DI group (n = 29)		C group (n = 15)	
		Before intervention	After intervention	Before intervention	After intervention
Energy	(kcal)	2136.2 ± 644.5	1942.4 ± 638.1$^{\$\$}$	1914.2 ± 355.3	1799.8 ± 456.0
Energy/ energy requirement	(%)	115.3 ± 31.6	104.8 ± 31.7$^{\$\$}$	109.7 ± 25.5	102.9 ± 27.9
Protein/energy	(%)	14.9 ± 2.5	15.0 ± 2.4	14.2 ± 2.0	14.2 ± 2.7
Fat/energy	(%)	28.3 ± 6.3	28.0 ± 5.6	28.7 ± 7.8	29.9 ± 6.7
Carbohydrates/ energy	(%)	54.9 ± 14.6	53.4 ± 7.1	49.9 ± 8.5	50.1 ± 10.4
Ni	(μg)	193.4 ± 89.6	121.3 ± 60.9$^{\$\$}$	144.6 ± 84.5	99.6 ± 71.0$^{\#\#}$
Co	(μg)	3.3 ± 2.2	1.8 ± 1.9$^{\$\$}$	3.6 ± 3.8	1.5 ± 1.8
Cr	(μg)	117.0 ± 30.6	105.5 ± 31.9$^{\$\$}$	99.9 ± 21.4	90.9 ± 23.8
Sn	(μg)	693.7 ± 223.4	603.8 ± 209.3$^{\$\$}$	616.5 ± 215.3	545.9 ± 183.3$^{\#}$
Ni/energy	(ng/kcal)	0.093 ± 0.041	0.063 ± 0.033$^{\$\$}$	0.072 ± 0.034	0.053 ± 0.034$^{\#}$
Co/energy	(ng/kcal)	0.002 ± 0.001	0.001 ± 0.001$^{\$\$}$	0.002 ± 0.002	0.001 ± 0.001
Cr/energy	(ng/kcal)	0.056 ± 0.011	0.055 ± 0.010	0.053 ± 0.010	0.052 ± 0.011
Sn/energy	(ng/kcal)	0.328 ± 0.066	0.316 ± 0.073	0.324 ± 0.104	0.304 ± 0.068

Values are the mean ± standard deviation. $^{\$}p < 0.05$, $^{\$\$}p < 0.01$ vs. the DI group before the dietary intervention; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. the C group before the intervention. Data were analyzed by the paired t-test (energy, energy/energy requirement, Ni, Cr, and Sn in the DI group, and Sn in the C group) or the Wilcoxon signed-rank test (others). DI, dietary intervention; C, control; Ni, nickel; Co, cobalt; Cr, chromium; Sn, tin.

A detailed comparison of findings in the DI group with previous studies is as follows. Watanabe et al. (7) reported that the intake of Ni in the general Japanese population was 110–175 μg/day, which is lower than that in the general population in Europe and in the United States (120–4,500 μg/day). However, the Ni intake in this study, 145–193 μg/day, is similar to that in Europe and in the United States (3, 7). Higher Cr and Sn intake levels were reduced by the intervention, but they were still higher than those in the general population in Japan. However, the intake of Co was lower than that in the general population in Japan.

There is a relatively high level of Ni and Co in characteristic food products, such as nuts, beans, and algae (seaweed). Our patients were able to avoid these food products using the materials presented in the dietary intervention program. However, in some cases, the patients did not realize that food products that are normally served as side dishes used in Japanese cuisines (e.g., those based on soybean products, soybeans in the pod, or broad beans, such as fermented soybeans or deep-fried tofu) should be restricted. The intake of Cr and Sn was decreased with the dietary intervention, but the energy intake rate of these intakes did not change. One of the reasons for this finding is as follows. Cr and Sn are contained in foods that are used daily, such as carbohydrate-rich foods (e.g., rice and bread) and protein-rich foods (e.g., meat, seafood, beans, and eggs). Therefore, a specific method for restricting the intake of Cr and Sn should be carried out in the future.

In this study, Ni intake in the C group was lower than that in the DI group, but the improvement of symptoms was less. Additionally, the DI group showed a decrease in all four metals with improved symptoms. This discrepancy in findings between groups may be because clinical symptoms result from an interaction among positive metals.

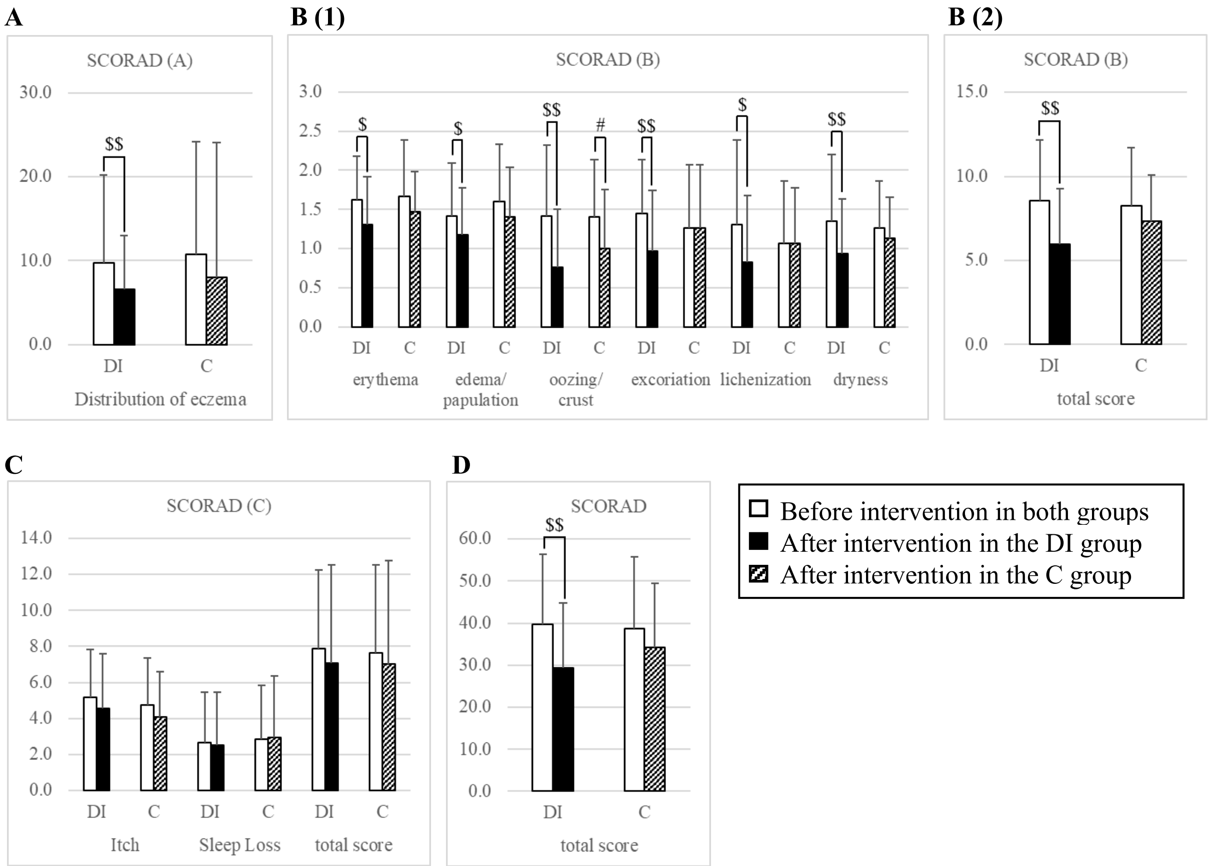

Figure 3. Skin symptoms and the SCORAD index.

A: Distribution of eczema, ranging from 0% to 100% of the body's surface involved. B: Severity of symptoms. Grades of 0–3 include erythema, edema/papulation, oozing/crust, excoriation, lichenization, and dryness. C: Subjective scale of daily itching and somnolence, ranging from 0 to 10, with a maximum total score of 20. D: Total SCORAD score, which was calculated as follows: SCORAD = A/5 + 7B/2 + C. (26). Data are expressed as the mean ± standard deviation. $^{\$}p < 0.05$, $^{\$\$}p < 0.01$ vs. the DI group before the dietary intervention; $^{\#}p < 0.05$ vs. the C group before the intervention. Data were analyzed by the paired t-test (total SCORAD [B] score, total SCORAD score) or the Wilcoxon signed-rank test (others). SCORAD, Severity Scoring of Atopic Dermatitis; DI, dietary intervention; C, control.

The performance of such strict metal-restricted diets should be limited to a period of 1 month because this diet can cause a deficiency in trace elements (8). In this study, we experienced difficult conditions in maintaining the dietary intervention program because of some events, such as a sudden meal consumed during a trip or an unexpected hospitalization. The achievement of any improvement takes a certain amount of time, but the recurrence of symptoms does not take much time. In this study, we used a 1-month period of intervention, but a longer dietary intervention period may be required for some patients with a metal allergy.

The effective results of the dietary intervention in this study indicate that more complete guidelines based on scientific knowledge of the food products that contain metals, as well as nutrition and cooking methods, designed to match the dietary lifestyle of the various patients are required. Dietary intervention by a registered dietitian is effective for improving skin symptoms with a reduction in metal intake. Our findings suggest the importance of intervention programs conducted by registered dieticians.

STUDY LIMITATIONS AND FUTURE PROSPECTS

This controlled study showed clear positive results of the dietary intervention with input by a registered dietician, but a multicenter trial will be required to confirm our results in the future. Further studies on the appropriate metal intake level and the continuation of dietary treatment methods are also required. The metal content of various food products should be included in the standard labels for related products similar to non-metal nutritional contents. An easy and convenient dietary intervention by a registered dietician can achieve restriction of metals using the standard labels for related products. Additionally, the effectiveness of a detailed dietary intervention by registered dieticians for patients with a systemic metal allergy should be recognized by medical doctors, especially dermatologists. A systematic and detailed dietary intervention for each positive metal in each patient should be required for further consideration and development. A great deal of time and effort was expended in this pioneer step of study, in both the intervention and calculation for the metal and nutritional content of the foods. The results of this study prove the requirement for the intervention by a registered dietitian. Further research for more effective interventions could be conducted and medical insurance coverage for dietary intervention for systemic metal allergy should be arranged in the near future. We analyzed the details of urinary metal excretion in this study with the expectation that assessment of urinary metal excretion might be a convenient and useful tool for detailed dietary intervention in the future.

Table IV. Blood test results

		DI group (n = 29)		C group (n = 15)	
		Before intervention	After intervention	Before intervention	After intervention
WBCs	(× 10^2/µL)	65.0 ± 15.3	63.0 ± 15.9	74.0 ± 19.2	66.4 ± 20.5$^{\#}$
PLTs	(× 10^4/µL)	23.4 ± 5.6	22.9 ± 5.2	26.2 ± 5.4	26.8 ± 5.3*
CRP	(mg/dL)	0.16 ± 0.49	0.09 ± 0.14	0.11 ± 0.20	0.07 ± 0.08
AST	(U/L)	25.9 ± 10.5	25.2 ± 9.6	20.3 ± 4.5*	20.3 ± 4.9
ALT	(U/L)	25.3 ± 21.3	24.1 ± 21.5	18.1 ± 7.8	17.8 ± 8.6
γ-GTP	(U/L)	35.5 ± 34.3	30.6 ± 25.4$^{\$\$}$	22.8 ± 11.3	21.9 ± 11.8
BUN	(mg/dL)	14.9 ± 6.2	15.0 ± 6.0	12.2 ± 3.4	11.7 ± 3.6
Creatinine	(mg/dL)	0.8 ± 0.2	0.8 ± 0.2	0.7 ± 0.2	0.7 ± 0.2
eGFRcreat	(mL/min/1.73 m^2)	74.7 ± 18.6	74.6 ± 19.1	78.7 ± 19.1	78.9 ± 19.6
TP	(g/dL)	7.2 ± 0.5	7.1 ± 0.5	7.0 ± 0.4	7.0 ± 0.3
Alb	(g/dL)	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.3	4.3 ± 0.3
Glu	(mg/dL)	102.4 ± 17.8	100.0 ± 19.5	99.9 ± 24.0	104.3 ± 26.9
HDL-C	(mg/dL)	63.8 ± 16.7	62.6 ± 15.8	66.5 ± 19.9	63.9 ± 15.1
LDL-C	(mg/dL)	121.7 ± 34.0	119.4 ± 28.9	104.3 ± 31.5	107.1 ± 32.4
TG	(mg/dL)	138.3 ± 97.1	141.0 ± 96.5	157.5 ± 86.0	146.5 ± 88.4
TARC	(pg/mL)	1143.8 ± 1462.1	1147.2 ± 1914.0$^{\$}$	478.9 ± 231.8	560.6 ± 520.8
Number of eosinophils	(%)	5.9 ± 6.6	5.2 ± 5.2	3.8 ± 2.4	3.7 ± 2.2
LDH	(U/L)	207.9 ± 63.9	206.1 ± 69.5	174.0 ± 28.1*	177.0 ± 36.9
Non-specific IgE	(IU/mL)	514.7 ± 905.7	498.8 ± 870.8	857.3 ± 1743.1	805.3 ± 1632.8

Values are the mean ± standard deviation. *$p < 0.05$ vs. the DI group before or after the dietary intervention (Mann-Whitney U test for AST and LDH or the Student t-test for PLTs); $^{\$}p < 0.05$, $^{\$\$}p < 0.01$ vs. the DI group before the dietary intervention; $^{\#}p < 0.05$, $^{\#\#}p < 0.01$ vs. the C group before the intervention (Wilcoxon signed-rank test). DI, dietary intervention; C, control; WBCs, white blood cells; PLTs, platelet count; CRP, the C-reactive protein; AST, aspartate aminotransferase; ALT, alanine aminotransferase; γ-GTP, γ-glutamyl transferase; BUN, blood urea nitrogen; Cr, creatinine; eGFRcreat, estimated glomerular filtration rate creat; TP, total protein; Alb, albumin; Glu, glucose; HDL-C, HDL cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; TARC, thymus and activation-regulated chemokine; LDH, lactate dehydrogenase.

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The authors have no conflicts of interest to declare.

REFERENCES

1. Veien NK. Systemic contact dermatitis. Int J Dermatol. 2011;50(12):1445–1456.
2. Takayama K, Yokozeki H, Matsunaga K, Katayama I, Aiba S, Ikezawa Y, et al. Clinical practice guidelines for contact dermatitis 2020. Jpn J Dermatol. 2020;130:523–567. Japanese.
3. Pizzutelli S. Systemic nickel hypersensitivity and diet: myth or reality? Eur Ann Allergy Clin Immunol. 2011;43(1):5–18.
4. Fabbro SK, Zirwas MJ. Systemic contact dermatitis to foods: nickel, BOP, and more. Curr Allergy Asthma Rep. 2014;14(10):463.
5. Pizzutelli S. Reply to: Update on systemic nickel allergy syndrome and diet. Eur Ann Allergy Clin Immunol. 2015;47(1):27–32.
6. Adachi A. The diagnosis of metal contact allergy and systemic metal allergy. J Environ Dermatol Cutan Allergol. 2011;5:1–10. Japanese (Abstract and tables in English).
7. Watanabe T, Kataoka Y, Hayashi K, Matsuda R, Uneyama C. Dietary exposure of the Japanese general population to elements: Total Diet Study 2013-2018. Food Saf (Tokyo). 2022;10(3):83–101.
8. Jensen CS, Menne T, Lisby S, Kristensen J, Veien NK. Experimental systemic contact dermatitis from nickel: a dose-response study. Contact Dermatitis. 2003;49(3):124–132.
9. Hamamoto Y, Shide K, Harada N, Tanioka M, Miyaji Y, Harashima S, et al. A case of effective nickel-restricted diet for nickel systemic contact dermatitis. J Metabol Clin Nutr. 2014;17:249–253. Japanese (Abstract in English).
10. Stuckert J, Nedorost S. Low-cobalt diet for dyshidrotic eczema patients. Contact Dermatitis. 2008;59(6):361–365.
11. Sharma AD. Low chromate diet in dermatology. Indian J Dermatol. 2009;54(3):293–5.
12. Grundler F, Seralini GE, Mesnage R, Peynet V, Wilhelmi de Toledo F. Excretion of heavy metals and glyphosate in urine and hair before and after long-term fasting in humans. Front Nutr. 2021;8:708069.
13. Darsow U, Fedorov M, Schwegler U, Twardella D, Schaller KH, Habernegg R, et al. Influence of dietary factors, age and nickel contact dermatitis on nickel excretion. Contact Dermatitis. 2012;67(6): 351–358.
14. Ministry of Education, Culture, Sports, Science and Technology of Japan. Standard tables of food composition in Japan -2015- (Seventh Revised Version) pdf. [Internet]. 2016 [cited 2022 Dec 12]. Available from:
https://www.mext.go.jp/en/policy/science_tech-nology/policy/title01/detail01/1374030.html.
15. Suzuki Y, Tanushi S. Table of trace element contents in Japanese foodstuffs. Tokyo: Daiichishuppan; 1993.
16. Adachi A, Horikawa T, Takashima T, Komura T, Tani M, Michihashi M. Potential efficacy of low metal diets and dental metal elimination in the management of atopic dermatitis: an open clinical study. J Dermatol. 1997;24(1):12–19.
17. Adachi A. Clinical Feature and examination of contact dermatitis. Arerugi. 2021;70(3):156–164. Japanese.
18. Ministry of Health, Labor and Welfare of Japan. Dietary Reference Intakes for Japanese (2015). [Internet]. 2015 [cited 2022 Dec 12]. Available from:
https://www.mhlw.go.jp/file/06-Seisakujouhou-10900000-Kenkoukyoku / Full_DRIs2015.pdf.
19. Kato E, Takachi R, Ishihara J, Ishii Y, Sasazuki S, Sawada N, et al. Online version of the self-administered food frequency questionnaire for the Japan Public Health Center-based Prospective Study for the Next Generation (JPHC-NEXT) protocol: Relative validity, usability, and comparison with a printed questionnaire. Journal of Epidemiology. 2017;27:435–446.
20. Araki E, Goto A, Kondo T, Noda M, Noto H, Origasa H, et al. Japanese Clinical Practice Guideline for diabetes 2019. Diabetol Int. 2020;11(3):165–223.
21. Kinoshita M, Yokote K, Arai H, Iida M, Ishigaki Y, Ishibashi S, et al. Japan Atherosclerosis Society (JAS) guidelines for prevention of atherosclerotic cardiovascular diseases 2017. J Atheroscler Thromb. 2018;25(9):846–984.
22. Saeki H, Ohya Y, Furuta J, Arakawa K, Ichiyama S, Katsunuma T, et al. Guideline for Management of Atopic Dermatitis 2021. Jpn J Dermatol. 2021;131:2691–2777. Japanese.
23. Furue M, Saeki H, Furukawa F, Hide M, Ohtsuki M, Nakamura T, et al. Guideline for Management of Atopic Dermatitis. Jpn J Dermatol. 2008;118:325–342. Japanese.

24. No authors listed. Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186(1):23–31.
25. Yamaguchi H, Hirasawa N, Asakawa S, Okita K, Tokura Y. Intrinsic atopic dermatitis shows high serum nickel concentration. Allergol Int. 2015;64(3):282–284.
26. Panahi Y, Davoudi SM, Madanchi N, Abolhasani E. Recombinant human interferon gamma (Gamma Immunex) in treatment of atopic dermatitis. Clin Exp Med. 2012;12(4):241–245.

Appendix 1. Food products containing metals

	Nickel	Cobalt	Chromium	Manganese	Zinc	Copper
Beans	All beans	All beans	All beans	All beans	All beans	All beans
Nuts	All nuts	All nuts	All nuts	All nuts	All nuts	All nuts
Grains	Unpolished rice Buckwheat Oatmeal	Unpolished rice Buckwheat Oatmeal	Unpolished rice Buckwheat Oatmeal	Unpolished rice Wheat	Unpolished rice Wheat	Unpolished rice
Meat	Liver	Liver	Liver	Liver	Liver	Liver
Sea foods	Oyster Shellfish	Oyster Shellfish	Oyster Shellfish		Oyster Crab Octopus	Oyster
Spices	All spices	All spices	All spices	All spices	All spices	
Beverages	Cocoa Wine	Cocoa Beer	Cocoa	Tea Cocoa	Cocoa	Tea Cocoa
Sweets	Chocolate	Chocolate	Chocolate	Chocolate	Chocolate	Chocolate

The list includes foods that contain large amounts of each metal (17, 22). However, tin is not listed because the criteria for listing are not clear, but dermatologists use this table. Patients with hypersensitivity to each metal should avoid eating the foods listed in this table.

Appendix 2. Food containing metals

μg/100 g

Food group	Foods	Nickel	Cobalt	Chromium	Tin
1. Cereals	Soba, buckwheat noodle (raw, wet form)	85	8	34	160
	Oats (whole grain with hull)	160	0	34	37
	Proso millet (milled grain)	220	0	22	200
	Wheat germ	140	0	60	1,300
4. Confectioneries	Chocolate (sweet)	260	0	42	430
6. Nuts and seeds	Sweet almonds (dried)	180	0	30	0
	Cashew nuts, roasted and salted	370	0	29	0
	Walnuts, roasted	510	0	30	0
	Coconuts, dried	1,400	0	21	0
	Brazil nuts, roasted	380	51	75	510
	Hazelnuts, roasted	360	0	32	360
	Pecans, roasted	130	0	∅	330
	Macadamia nuts, roasted and salted	110	0	31	420
	Pine nuts, roasted	150	0	42	0
	Sesame seeds (dried)	230	0	31	0
	Peanuts (dried)	820	7	33	0
	Chestnuts (raw)	270	0	10	5
	Chestnuts (roasted)	220	0	∅	190
7. Pulses	Soybeans (domestic, whole, dry)	590	0	26	0
	Kinako, roasted and ground	1,000	0	43	830
	Natto, fermented soybeans (itohiki-natto)	320	0	14	430
	Miso (soybean-koji miso)	270	0	23	320
	Adzuki beans (whole, dry)	440	14	21	0
	Kidney beans (whole, dry)	180	23	43	0
	Peas (whole, dry)	160	13	43	0
	Cowpeas (whole, dry)	470	25	23	370
8. Fish and shellfish	Short-necked clam (tsukudani)	110	0	74	480
	Short-necked clam (canned with brine; solids)	57	22	55	330
	Hard clam (raw, uncooked)	120	30	27	0
	Hard clam (canned with seasoning; solids)	68	0	20	540
	Squid and cuttlefish (surume, dried)	130	0	33	450
	Crabs (wary crab)	0	20	12	0
	Sea urchin (raw gonads)	150	17	35	0
	Sardines (boiled and dried)	49	0	96	1,700
	Sardines (tazukuri, dried small anchovy)	∅	0	110	1,800
	Eel (viscera)	0	22	11	88
	Merluce or hake (raw)	420	0	10	0

Appendix 2. Food containing metals (continued)

μg/100 g

Food group	Foods	Nickel	Cobalt	Chromium	Tin
12. Vegetables	Bamboo shoots (shoots, raw)	100	0	15	27
	Bracken (fresh, raw)	140	13	9	0
	Bracken (dried)	330	130	29	1,100
	Edamame, green soybeans (beans, immature, raw)	96	5	19	0
	Peas, garden peas (green peas)	160	4	7	0
	Perilla (leaves)	110	0	19	0
	Perilla (seeds)	390	20	28	0
	Maize, corn (whole grain)	40	7	23	100
	Maize, corn (popcorn, popped)	61	0	48	230
13. Fruits	Kaki, Japanese persimmon (raw fruit)	62	0	3	0
	Limes (raw juice)	65	0	3	0
14. Fungi	Shiitake (dried, uncooked)	∅	0	31	16
	Nameko (raw, uncooked)	140	0	3	0
	Hiratake (raw, uncooked)	180	0	12	0
15. Algae	Hijiki (boiled and dried)	260	87	270	0
	Sea lettuce (dried)	0	0	85	2,200
	Green laver (dried)	870	170	480	0
	Konbu, kelp (shio-konbu)	230	0	63	1,200
	Stipe and center vein (raw)	150	23	99	0
16. Beverages	Cocoa (pure cocoa)	610	97	180	0
	Coffee (instant)	99	0	∅	730
	Tea (hojicha, roasted, tea)	570	13	110	0
	Tea (oolong tea, tea)	280	16	65	0
	Tea (black tea, Tea)	480	23	49	0
	Tea (sencha, common grade, tea)	650	0	79	0
	Tea (maccha, finely ground)	740	0	92	0
	Tea (genmaicha, tea)	230	15	35	0
	Mugicha, roasted barley, grain	670	0	41	0
17. Seasoning and spices	Curry (powder)	87	0	70	930
	Clove powder	90	46	170	850
	Pepper (black)	71	0	29	550
	Japanese pepper	480	0	88	780
	Sage powder	280	0	230	1,800
	Thyme powder	140	0	220	1,600
	Paprika powder	140	0	95	1,600
	Yeast, baker's yeast (dried)	0	75	51	440

A summary table of foods with a high content of nickel, cobalt, chromium, or tin per 100 g of the edible portion from the trace element content table published in the contact dermatitis clinical practice guideline (2) followed by a book edited by Yasuo Suzuki (1993) (15). ∅ indicates below the quantification limit. The order of metals was modified by the authors.

Appendix 3.

Your nutritional needs of a day

Date		**Name**		
Standard body weight kg		**Energy** kcal		**Salt** g

	FOOD	BREAKFAST	LUNCH	DINNER
1	 Rice Bread Noodle Potato Pumpkin	Bread ☐ g or Rice ☐ g or	Bread ☐ g or Rice ☐ g or	Bread ☐ g or Rice ☐ g or
2	60g lean meat or A piece of fish or 100g tofu or An egg 	You choose	You choose	You choose
3	Vegetables Sea weeds mushrooms 	Not less than 100g	Not less than 100g	Not less than 100g

Fatty foods no more than tablespoons of ☐. (You had better choose vegetable oil.) 

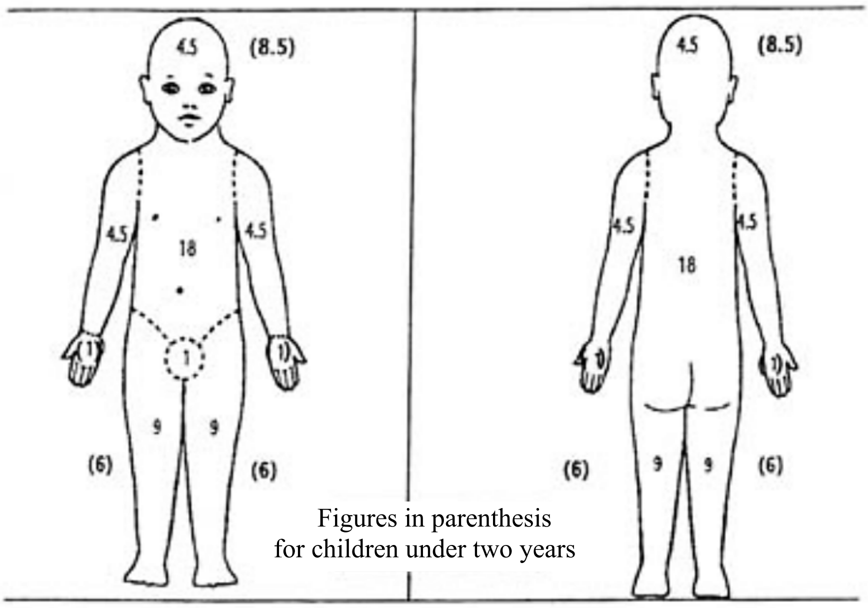
Fruit; Half an apple.

Low fat milk ☐cc. 

Educational materials for the dietary intake provided to patients used in Kobe University Hospital.
Registered dietitians instructed patients to eat a nutritionally balanced diet. They recommended eating grain dishes such as rice, bread, and noodles, main dishes such as meat, fish, eggs, and soybean products, and side dishes such as vegetables.

Appendix 4. Severity Scoring of Atopic Dermatitis (SCORAD)

Distribution of eczema (%) (A) A ( ) %



Judgment of intensity of skin eruption (B) (0: None, 1: Mild, 2: Moderate, 3: Severe) B ( ) / 18points

erythema ( )
edema/papulation ( )
oozing/crust ( )
excoriation ( )
lichenization ( )
dryness ( )

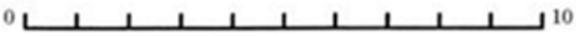
The intensity of skin eruption is scored by selecting the average site for each item.

Scoring is based on the area without skin eruption.

Subjective symptoms (C) Average value for the last 3 days. C ( ) / 20points

Itch

Sleep Loss



SCORAD A/5 + 7B / 2 + C = ___________ / 103points