Original Article

Children with atopic dermatitis in Daejeon, Korea: individualized nutrition intervention for disease severity and nutritional status

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Background and Objectives: Atopic dermatitis is one of the most common pediatric chronic inflammatory skin diseases, and certain food allergens and nutrients are closely related to the development and severity of atopic dermatitis. While avoidance of the causative foods is considered the mainstay of treatment, unverified excessive restriction might induce unnecessary limitations in the food intake, consequently leading to nutritional deficiencies and poor growth. This study aimed to identify the characteristics and nutrient intake status in children with atopic dermatitis and to investigate the effects of individualized nutrition intervention. **Methods and Study Design:** We retrospectively reviewed electronic medical records of 77 pediatric patients with atopic dermatitis who received 4 months of individualized nutrition intervention combined with an elimination diet. The patient characteristics, nutrient intake status, and clinical status were examined before and after the intervention. **Results:** Before the intervention, 5 children had a weight for height z-score below -2.0, and 48.1% had experienced food restriction; these children showed a significantly higher SCORing of Atopic Dermatitis index than those without experiences, with the number of restricted foods before the intervention positively correlating with the disease severity. The intakes of n-6 and n-3 fatty acids, calcium, folate, and vitamin D were lower than the recommended nutrient intakes for Koreans. After the intervention, the weight for height z-score of 35 children was significantly increased and their SCORing of Atopic Dermatitis index was significantly reduced (p<0.05). **Conclusions:** Individualized nutrition intervention appears useful for alleviating the severity of atopic dermatitis and improving the growth status by improving the nutrient intake.

Key Words: atopic dermatitis, individualized nutrition intervention, SCORAD index, growth, nutritional status

INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin diseases, and frequently begins already in early infancy.[1] Although it varies between different regions, the prevalence of childhood eczema or AD is continuously increasing worldwide. The 2003 National Survey of Children's Health in the US showed that the lifetime prevalence of AD was 10.7% in children under 18 years,[2] while the International Study of Asthma and Allergies in Childhood reported one-year prevalence rates of up to 20% in Australasia, England, and Scandinavia.[3] Further, the Korea National Health and Nutrition Examination Survey data showed an AD rate of 13.0% in children aged 1 to 18 years.[4]

Numerous trigger factors of AD have been verified in recent decades, including genetic factors,[5] inhaled allergens, food allergens and certain nutrients,[6] irritating substances, and infectious microorganisms.[7] Of these factors, the major food allergens, including egg white, cow's milk, soybeans, wheat, and peanuts, have been reported to be more strongly related to AD in childhood than in adults.[8,9] The clinical spectrum of food allergy (FA) ranges from mild skin irritation to severe life-threatening anaphylaxis,[10] and AD secondary to FA includes skin disorders such as incessant pruritus, xerosis, eczematous lesions, and lichenification.

These various skin symptoms of AD secondary to FA are caused by adverse cellular responses activated through specific antibodies against the food allergen,[11] mediated by both immunoglobulin E (IgE) and non-IgE mechanisms. It has been demonstrated that IgE-mediated FA appears as acute reactions such as localized urticaria and anaphylaxis, whereas non-IgE-mediated FA usually results in delayed respiratory, gastrointestinal, and cutaneous symptoms.[12] Moreover, while it has been well established that IgE-mediated FA plays a central role in the immunopathogenesis of AD,[13] non-IgE-mediated responses have also been recently reported as a major characteristic of AD. Direct exacerbation of AD with devel-

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opment of new eczematous outbreaks tends to occur more frequently as a delayed reaction, whereas the immediate reactions to IgE-mediated FA often include increased scratching and secondary exacerbation of eczematous lesions.[14]

Importantly, in addition to discriminating between IgE-mediated and non-IgE-medicated reactions in AD, it should be noted that AD patients with FA may be allergic to multiple food allergens.[15] Although numerous treatment options are currently being investigated, AD associated with FA can be successfully controlled with dietary avoidance and individualized restriction of foods containing sensitized allergens.[16] Unfortunately, the typical food allergens, such as milk, fish, eggs, wheat, soybeans, and peanuts, are rich in important nutrients, especially for actively growing children. Various studies have reported possible risks of growth delay and nutritional deficiencies, consequently causing weight loss and damage to the immunomodulatory system, as a result of avoidance of these foods, which in turn exerts negative effects on the progress, treatment, and prognosis of the disease.[17,18] Due to the risk of such nutritional deficiencies, well-planned and individualized supervision over these diets is vital, particularly if the avoided foods are rich in essential nutrients needed for growth. Adequate nutrient supply through proper intake of alternative foods is required for the prevention of nutritional deficiency caused from excessive food elimination, and individual consideration should be taken to ensure a nutritionally adequate diet, especially for those with multiple food allergens.[10]

In addition to preventing malnutrition and maintaining proper dietary intake in children with AD secondary to FA, the effects of individualized nutrition interventions have also been researched. Although some of the previous studies implementing nutrition education programs for children with AD have shown that they were effective in reducing the severity of AD and serum cytokine levels and for maintaining dietary balance,[19,20] these studies only included educational programs and did not take into account the effects of combined dietary restriction. For further improvements in the AD status and to concurrently ensure the consumption of sufficient nutrients for normal growth, individualized nutrition intervention should be executed along with food restriction. With this in mind, the aim of this study was to identify the factors related to the severity of AD and nutrient status in pediatric AD patients with FA and to demonstrate the effects of individualized nutrition intervention in these patients. Further, we also aimed to provide basic information that can be used as a basis for the establishment of appropriate dietary guidelines for children with AD.

MATERIALS AND METHODS

Study design and sample size

This study was a retrospective study of electronic medical records with the aim to evaluate the effects of 4-month individualized nutrition interventions implemented along with an elimination diet. Each individually modified and restricted diet was maintained during the whole period of time, with the individualized nutrition intervention carried out as 1-hour sessions, once a month over a period of 4 months, including an initial session for each subject and caregiver, for a total of 5 times. At the beginning of the intervention, the caregivers were trained in appropriate bathing and skin care practices, and received instructions regarding the application of topical emollients. Use of topical steroids was limited.

The sample size was calculated based on the results of previous studies reporting that a 30% reduction in the SCORing of Atopic Dermatitis (SCORAD) index was considered to indicate an effect of nutrition intervention on the severity of disease. Using PS-Power and Sample size Calculation v3.0 (Informer Technologies, Inc.) applied with the paired *t*-test along with a 5% significance level and 80% power, at least 20 children were determined to be required. With an expected drop-out rate of 20%, an initial sample size of over 30 children was ultimately considered necessary.

Subjects

A total of 77 children aged 4 months to 16 years diagnosed with AD and FA according to the diagnostic criteria proposed by Hanifin and Rajka,[21] treated between March 2011 and December 2012 at the Pediatric Allergy Clinic, Chungnam National University Hospital, Daejeon, Korea, were included in this study. The electronic medical record database analyzed consisted of anonymous disease-related information and the diet records of the subjects without any exposure of private information. This study was approved by Institutional Review Board of Chungnam National University.

Exclusion criteria

Children who took oral steroids due to severe flare-ups and/or who had infectious diseases that made the interpretation of outcomes difficult during the individual intervention periods, and children who did not attend all 5 sessions of nutrition intervention were excluded from the final analysis.

Anthropometric measurements

The subjects' height and weight were measured and recorded bimonthly using the following measuring methods: for children under 24 months, the height and weight were measured with the child in a recumbent position, with the shoes off and with a light top on, using an automated height and weight measuring instrument. For children aged over 24 months, the height and weight were measured to the nearest 0.1 cm with the child in a standing position, with the shoes off and with a light top on, using an automated height and weight measuring instrument. The growth and nutritional status were evaluated by the z-scores of the 2007 Korean National Growth Charts using the LMS parameters provided by the Korean Centers for Disease Control, where L is the power in the Box-Cox transformation, M is the median, and S is the generalized coefficient of variation.[22] The normal values of Korean children and adolescents reported by the Korean Pediatric Society in 2007 were used as the reference values. The standard deviations for weight for age (WAZ), height for age (HAZ), and weight for height (WHZ) were expressed as z-scores. WAZ, HAZ, or WHZ less than −2.0 represents moderate to severe under-nutrition.[23]

Assessment of the severity of AD

The clinical severity of AD was evaluated using the SCORAD index, a system commonly used worldwide to assess the severity of atopic eczema by medical staffs.[24] Besides the SCORAD index, the total serum IgE level and percent of serum eosinophils fraction (percent of total leukocytes), suggested as indices for evaluating the severity of AD,[25,26] were also measured. The total serum IgE (IU/mL) and food-specific IgE (KU/L) levels for representative food allergens (egg white, milk, peanut, soybean, wheat, and fish) were measured at 0 and 4 months using UniCAP (Pharmacia & Upjohn Diagnostics AB, Uppsala, Sweden). A serum level of 0.35 KU/L was determined as the cutoff value of undetectable food-specific IgE by the manufacturer.

Elimination diet and food challenge

An elimination diet preceded the food challenge in all children for the eight tested major allergic foods (milk, eggs, soybeans, wheat, beef, pork, chicken, and fish). The subjects were asked to avoid the suspected food allergen and everything containing that allergen according to their past history of allergic responses, skin prick tests, and food-specific IgE levels. Although the effects of breast milk and maternal diet on the development or severity of AD in children is controversial, if an infant fed with breast milk had food-specific IgE levels for milk that met the food allergy decision point,[27] the mother of the infant was asked to control her food intake or change to hydrolyzed formula feeding. Alternative foods were recommended for the maintenance of balanced nutrition, and foods not showing any allergic symptoms on the oral food challenge tests were permitted for consumption. To confirm the compliance of the elimination diet, all children or caregivers were required to record 3-day dietary diaries, including of two weekdays and one weekend day, per month.

Individualized nutrition intervention

For each child, individualized nutrition interventions (1 hour each) were performed 5 times, including an initial session, once a month for 4 months. Each intervention session was carried out with five common themes for all children, namely 1) the elimination diet and alternative foods for allowing adequate nutritional status, 2) increasing consumption of high-antioxidant foods, 3) adequate intake of foods containing n-3 fatty acids, 4) better choices of the child's favorite foods, and 5) a summary of the sessions and evaluations, and individually modified dietary recommendations in reference to their intakes, as analyzed using their diet records.

Dietary intake analysis

The one-day dietary intake was recorded at the first session using the 24-hour recall method with the help of a dietitian. At this session, children who were able to write, along with all caregivers, received an explanation about how to record the dietary diaries and how to measure the consumed amount of food from the dietitian. Subsequently, 3-day dietary diaries were recorded each month, as described above, mainly by the caregivers or children together with their caregivers. The submitted diaries were analyzed using Can-Pro 3.0 (The Korean Nutrition Society, Seoul, Republic of Korea) by a trained dietitian. The percent ratio of energy and nutrient intake to the recommended intake in the 2010 Dietary Reference Intakes for Koreans[28] (%KDRIs, calculated as [nutrient intake ÷ RNI or AI] × 100) was comparatively analyzed using the Recommended Nutrient Intake (RNI) or Adequate Intake (AI) of the KDRIs.

Statistical analysis

Continuous variables such as age, demographic and clinical characteristics, and severity of AD using the SCORAD index are expressed as means ± standard deviations and were analyzed using descriptive statistics after the Kolmogorov-Smirnov and Shapiro-Wilk normality tests. For comparisons of the SCORAD index according to various characteristics, the Mann-Whitney U test was used for non-normally distributed data. The nutrient intake and %KDRIs are shown as the means ± standard deviations and were analyzed using descriptive statistics after the Kolmogorov-Smirnov and Shapiro-Wilk normality tests. The correlations between clinical indices for AD and different characteristics were assessed using Spearman non-parametric correlation analysis, and the correlations between clinical indices and nutrient intake were analyzed by partial correlation analysis. Changes in the nutrient intake and severity of AD were assessed using the paired t-test for normally distributed data and Wilcoxon's matched-pairs signed-ranks test for non-normally distributed data. All statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA) version 21.0, and a value of p-value <0.05 was considered statistically significant for all analyses.

RESULTS

Demographic and clinical characteristics of the subjects

A total of 77 pediatric patients (42 boys [54.5%] and 35 girls [45.5%]; mean age, 3.84±3.80 years; range, 0.34–15.9 years) attending the individualized nutrition interventions were selected as subjects for this study and their medical records were retrospectively analyzed. The mean HAZ, WAZ, and WHZ were 0.01±1.14, -0.09±0.99, and -0.19±1.09, respectively. Two and five subjects had WAZ and WHZ <-2.0, respectively. The mean age at AD onset was 1.50±2.76 years, and 19.5% of the patients had family histories of AD and other allergic diseases such as asthma and rhinitis. The mean duration of breast milk feeding was 0.72±0.5 years. Further, 48.1% of the subjects had experiences of food restriction trials, and 27.8% had received previous nutrition intervention.

Most clinical characteristics showed non-parametric distributions. The mean total serum IgE level was 622±1,319 IU/mL. The mean food-specific IgE levels for egg white, milk, peanuts, soybean, wheat, and fish were 14.8±27.5, 8.22±23.4, 9.52±24.0, 7.37±19.1, 8.97±23.6, and 2.34±9.00 KU/L, respectively. The mean SCORAD index and the percent of serum eosinophils were 34.0±15.2 and 6.80±5.63, respectively. No significant differences in the non-normally distributed variables were observed between boys and girls (Table 1).

Table 1. Baseline demographic and clinical characteristics of the study subjects

	Total (n=77)	Boys (n=42)	Girls (n=35)
Demographic characteristics			
Age (years)	3.84±3.80 (0.34-15.9)	3.21±0.48 (0.34-12.9)	4.83±0.77 (0.44-15.9)
Height (cm)	97.4±27.3	93.5±3.65	103±5.36
Weight (kg)	17.1±12.1	14.9±1.30	19.8±2.60
Z-score for growth status			
Height for age†	0.01±1.14 (-2.03-3.53)	0.06±0.19 (-1.86-3.53)	0.07±0.18 (-1.73-2.34)
Weight for age†	-0.09±0.99 (-2.47-1.96)	-0.10±0.15 (-1.78-1.77)	-0.15±0.19 (-2.47-1.96)
Weight for height†	-0.19±1.09 (-2.81-2.48)	-0.23±0.15 (-1.84-1.40)	-0.27±0.20 (-2.81-1.81)
History of allergic disease			
Age of AD onset (years)	1.50±2.76 (0.01-15.0)	1.06±1.52 (0.01-4.50)	2.00±3.68 (0.01-15.0)
Family history of allergic disease, n (%)			
Paternal history of AD	4 (5.1)	2 (4.7)	2 (5.6)
Paternal history of other allergic disease	11 (15.0)	5 (11.6)	6 (16.7)
Maternal history of AD	9 (12.2)	4 (9.3)	5 (13.9)
Maternal history of other allergic disease	14 (17.8)	7 (16.2)	7 (19.5)
Sibling's history of AD	9 (12.2)	5 (11.6)	4 (11.1)
Sibling's history of other allergic disease	6 (7.6)	3 (7.0)	3 (8.4)
Duration of breast milk feeding (years)	0.72±0.51 (0.01-2.50)	0.75±0.09 (0.01-2.50)	0.68±0.08 (0.04-1.64)
Food restriction experience, n (%)	38 (48.1)	17 (39.5)	21 (58.4)
Numbers of food restricted	1.07±1.59 (0-6)	1.05±1.81 (0-6)	1.09±1.31 (0-4)
Previous nutrition intervention for AD, n (%)	22 (27.8)	10 (23.3)	12 (33.3)
Clinical characteristics			
SCORAD index	34.0±15.2	30.2±13.2	37.7±16.3
IgE (IU/mL)	622±1319 (0.26-7920)	664±1666 (5.74-7920)	572±757 (0.26-2814)
Food specific IgE (KU/L)			
Egg white	14.8±27.5	13.7±27.4	16.2±28.2
Milk	8.22±23.4	7.60±21.7	9.02±25.9
Peanut	9.52±24.0	7.27±19.5	12.43±29.0
Soybean	7.37±19.1	8.30±21.7	6.13±15.3
Wheat	8.97±23.6	8.45±24.4	9.63±22.9
Fish	2.34±9.00	2.17±7.55	2.56±10.8
% serum eosinophils (% in TLC)	6.80±5.63	6.08±4.53	7.63±6.66

AD: atopic dermatitis; IgE: immunoglobulin E; SCORAD: SCORing of Atopic Dermatitis; TLC: total leukocytes.
Data were calculated by descriptive statistics after the Kolmogorov-Smirnov and Shapiro-Wilk normality tests, and are presented as mean ±standard deviation or number (%), as appropriate.
†Normally distributed variables.

Table 2. Comparisons of the SCORAD indices according to different characteristics

	n	SCORAD index	Z	*p*-value
Paternal history of allergic disease	Yes (15)	30.7±13.8	-0.66	0.51
	No (60)	35.1±15.7		
Maternal history of allergic disease	Yes (23)	39.5±15.7	-1.90	0.049*
	No (53)	32.0±14.8		
Food restriction experience	Yes (38)	39.4±17.5	-2.72	0.00**
	No (39)	28.5±10.8		
Previous nutrition intervention for AD	Yes (22)	40.6±18.9	-1.90	0.049*
	No (52)	31.2±12.5		

SCORAD: SCORing of Atopic Dermatitis.
Data are presented as number and mean±standard deviation.
*,** Significant differences (*p<0.05 and **p<0.01) by the Mann-Whitney U test for non-normally distributed data.

Comparisons of the SCORAD index according to different characteristics

The SCORAD index, which indicates the severity of AD, was significantly higher in children with compared to without a maternal history of allergic disease (39.4±15.7 vs 32.0±14.8). Further, children who had a previous food restriction trial experience showed a significantly higher SCORAD index (39.4±17.5) than children without previous restriction (28.5±10.8), and a significant differences were observed in the SCORAD index between children having received (40.6±18.9) and not received previous intervention (31.2±12.5) (Table 2).

Intake of nutrients before the intervention

Seventy-three (94.8%) out of the 77 one-day diet records were analyzed. Four non-usable diet records were excluded from the analysis due to the reasons such as incomplete records, inaccurate amount of recorded foods, and extremely unusual food intake. Except the intakes of vitamin A and vitamin D, which showed non-normally distributed shapes, all data were considered parametric values.

Table 3. Intake of nutrients in subjects with atopic dermatitis before the individualized nutritional intervention (n=73)

	Amount of nutrient intake	% KDRIs
Energy, kcal	1,070±402	93.8±24.9‡
Protein, g	21.1±13.7	114±70.1
Lipid, g	31.9±15.7	27.5±10.6§
n-6 fatty acids, g	4.43±3.31	3.50±2.39§
n-3 fatty acids, g	0.48±0.42	0.39±0.34§
n-6/n-3	11.9±7.78	
Carbohydrate, g	159±64.9	71.4±21.5§
Dietary fiber, g	9.16±6.29	
C:P:F ratio /energy		
Ca, mg	439±250	93.8±67.3
P, mg	574±305	113±49.7
Fe, mg	7.70±4.21	107±49.1
Na, mg	1,857±1,240	
K, mg	1,612±752	
Zn, mg	5.32±2.04	142±50.6
Vit A, μgRE	555±587†	157±178†
Vit B-1, mg	0.66±0.40	130±65.0
Vit B-2, mg	0.74±0.38	121±70.4
Vit B-6, mg	1.12±0.65	173±84.8
Niacin, mg	8.04±4.09	132±61.8
Vit C, mg	95.6±64.4	204±146
Folate, mg	136±76.3	82.2±44.3
Vit E, mg	8.62±4.83	
Cholesterol, mg	143±144	
Vit D, μg	2.99±3.96†	60.7±79.6†

%KDRIs: percent ratio of energy and nutrients to the recommended intake in the 2010 Dietary Reference Intakes for Koreans; C: carbohydrate; P: protein; F: fat; Vit: vitamin.
Data were calculated by descriptive statistics after the Kolmogorov-Smirnov and Shapiro-Wilk normality tests, and are presented as mean±standard deviation.
†Non-normally distributed data.
‡% estimated energy requirement.
§% energy from the presented nutrient.

Table 4. Spearman correlation coefficients (*r*) between clinical indices for atopic dermatitis and different characteristics

	SCORAD index		Serum IgE		% serum eosinophils	
	r	*p*-value	*r*	*p*-value	*r*	*p*-value
Age of AD onset (years)	-0.24†	0.09	-0.24†	0.09	0.06	0.65
Duration of breast milk feeding (years)	-0.04	0.76	-0.07	0.61	-0.16	0.21
Number of foods restricted previously (n)	0.24*	<0.05	0.24	0.07	-0.06	0.62

AD: atopic dermatitis; SCORAD index: SCORing of Atopic Dermatitis; IgE: Immunoglobulin E.
†Partial correlation adjusted by age.
*Significant correlation between the clinical index and demographic characteristic ($p<0.05$).

The mean energy intake was 1,070±402 kcal, which was 93.8±24.9% of the estimated energy requirement based on the 2010 KDRIs. The mean protein intake was 21.1±13.7 g (114±70.1 %KDRIs). Most nutrient intakes met the recommended intake levels; however, the n-6 (3.50±2.39 g) and n-3 (0.39±0.34 g) fatty acid, calcium (439±250 mg), folic acid (136±76.3 mg), and vitamin D (2.99±3.96 μg) intake levels were less than the recommended intake levels (Table 3).

Correlations between demographic characteristics and clinical indices for AD

The relationships between demographic characteristics with the clinical indices (SCORAD index, total serum IgE, and percent serum eosinophils) are shown in Table 4. The number of restricted foods before the intervention showed a significant positive correlation with the SCORAD index (r=0.24, p<0.05). On the other hand, the age at AD onset and duration of breast milk feeding did not significantly correlate with any of the 3 clinical indices.

Correlation between nutrient intake before nutrition intervention and clinical indices for AD

Partial correlation analyses adjusted by age (years) and energy intake (kcal) showed that the SCORAD index was found to be negatively correlated with calcium intake (r=-0.30, p<0.05) but positively correlated with folate intake (r=0.28, p<0.05). The total serum IgE level showed significant negative correlations with the intakes of n-6 fatty acids, n-3 fatty acids, and vitamin E, whereas the percent serum eosinophils positively correlated only with zinc intake (Table 5).

Comparison of nutrient intakes before and after nutrition intervention

Among the 77 initial subjects, 35 (45.5%; mean age,

Table 5. Partial correlation coefficients (*r*) adjusted by age (years) and energy intake (kcal) between clinical indices for atopic dermatitis and intake of nutrients in subjects before the intervention (n=35)

	SCORAD index	Serum IgE	% serum eosinophils
n-6 fatty acids, g	-0.16 (0.23)	-0.46 (0.00)**	-0.17 (0.23)
n-3 fatty acids, g	-0.16 (0.23)	-0.31 (0.03)*	-0.16 (0.27)
Ca, mg	-0.30 (0.02)*	-0.15 (0.29)	-0.04 (0.80)
Fe, mg	-0.06 (0.70)	-0.07 (0.65)	0.12 (0.41)
Zn, mg	-0.17 (0.18)	-0.19 (0.18)	0.28 (0.05)*
Vit A, μgRE	-0.16 (0.23)	-0.04 (0.79)	-0.12 (0.40)
Vit C, mg	0.25 (0.06)	0.08 (0.56)	-0.20 (0.16)
Folate, mg	0.28 (0.03)*	-0.18 (0.20)	-0.11 (0.46)
Vit E, mg	-0.03 (0.83)	-0.42 (0.00)**	0.03 (0.82)
Vit D, μg	-0.07 (0.59)	-0.07 (0.62)	0.18 (0.20)

SCORAD index: SCORing of Atopic Dermatitis; IgE: Immunoglobulin E; Vit: vitamin.
*, **Significant correlation between the clinical index for atopic dermatitis and nutrient intake (*p<0.05 and **p<0.01).

3.75±3.57 years) completed all 5 individualized nutrition interventions. Forty-two (54.6%) subjects failed to complete the 5 intervention sessions due to patient withdrawal, missed visits, or being in a state of exclusion criteria, among others.

The energy, protein, total lipid, and carbohydrate intake levels showed no significant changes between before and after intervention, whereas significant changes were observed in the intake levels of n-6 fatty acids (4.42±3.43 to 2.09±1.99 g, p<0.01), n-3 fatty acids (0.48±0.45 to 0.18±0.20 g, p<0.01), sodium (1,880±1,205 to 1,382±820 g, p<0.01), and vitamin E (8.75±4.60 to 6.93±3.04 g, p<0.05). Furthermore, increasing trends in the iron and vitamin D intake levels were also observed. The component ratios of carbohydrates, lipids, and proteins to daily energy intake and the %KDRIs of each nutrient intake after intervention were similar to those before the intervention except for total lipids (27.6±14.3 to 21.2±7.83% in energy intake, p<0.01), n-6 fatty acids (3.23±2.08 to 1.70±1.40%, p<0.01), n-3 fatty acids (0.37±0.36 to 0.15±0.14%, p<0.01), sodium (220±112 to 159±76.3%, p<0.01), and vitamin E (157±65.1 to 123±53.9%, p<0.01), which were significantly decreased. Conversely, vitamin D showed an increasing trend, although it did not achieve significance (Table 6).

Changes in growth status and severity of AD between before and after the intervention

To investigate the usefulness of the individualized nutrition intervention for improving the growth status and reducing the severity of AD, the 3 z-scores (HAZ, WAZ, and WHZ) and 3 clinical indices were analyzed. WHZ was significantly increased after the intervention (0.02 to 0.20, p<0.05), whereas HAZ was significantly decreased (0.26 to 0.08, p<0.05) and WAZ did not differ between after and before the intervention (Figure 1). The total serum IgE level (622 to 438, Z=-1.49, p=0.14) and percent serum eosinophils (6.80 to 5.09, Z=-0.15, p=0.88) tended to decrease after the intervention, but were not statistically different. Conversely, the SCORAD index (34.0 to 19.0, Z=-5.50, p<0.05) was significantly reduced after the intervention (Figure 2).

DISCUSSION

AD is a one of the most common chronic inflammatory skin diseases in children, and its incidence rate has been greatly increasing in recent years. AD has been reported to significantly correlate with FA, which in turn has been reported to negatively affect the growth and nutritional status of the affected children in cases of excessive food restriction or elimination diets without alternative foods or a meticulous nutritional care plan to ensure adequate intake of nutrients.

Altered growth status of children with AD and/or FA has been demonstrated in various studies.[29,30] Although inadequate nutrient intake due to severe food restriction or unnecessary elimination diets is generally considered the primary reason for the altered growth status, other possible reasons should also be considered. Flammarion et al proposed that the potential loss of nutrients caused by continued allergic inflammation, abnormal intestinal permeability caused by noncompliance with the diet, and an additional undiagnosed allergy or antigen remnants in the substituted food were associated with the growth status of children with AD and FA.[31] Moreover, lower albumin levels in children with cow's milk protein allergy and AD compared to in healthy controls, even under similar protein intakes, have been reported,[32] and may be explained by the fact that the requirements for energy and protein might be increased in children with AD as they are needed for skin regeneration to compensate for the loss of skin components in AD.[33]

In this study, although severely poor growth or a significant correlation between food restriction and lack of growth was not observed, the finding that 5 out of 77 children had a WHZ under -2.0, which is considered as malnutrition status, might imply the need for nutrition intervention to ensure appropriate growth in pediatric AD patients. Previous studies reported that 11%[34] and 15.6%[35] of participants with AD implemented food restriction based on unproven information rather than a valid diagnosis, and the result that 48.1% of children in our study had experienced previous food restriction might hence imply that a proper guideline or nutrition intervention for adequate nutrient intakes and growth status in children with AD related to FA had not been conducted in these children. In addition, the rate of previous food restriction was relatively high in our children, despite the observation that, except for milk (7 KU/L), the mean values of the food-specific IgE levels to the major food allergens (egg white: 15, peanuts: 14, soybean: 65, wheat: 80, and fish: 20 KU/L) were below the corresponding

Table 6. Intake of nutrients in subjects with atopic dermatitis before and after 4 months of individual nutritional intervention (n=35)

	Amount of nutrient intake				%KDRIs			
	Before	After 4 months	*t* or *Z*[§]	*p*-value	Before	After 4 months	t or Z[§]	*p*-value
Energy, kcal	1,055±406	1,056±268	-0.03	0.98	95.0±28.4[†]	90.4±23.0[†]	0.91	0.37
Protein, g	22.7±14.6	23.9±16.9	-0.34	0.74	123±79.8	131±75.4	-0.45	0.66
Lipid, g	31.1±16.2	25.4±14.3	1.66	0.11	27.6±14.3[‡]	21.2±7.83[‡]	2.77	0.01[*]
n-6 fatty acids, g	4.42±3.43	2.09±1.99	4.83	0.00[*]	3.23±2.08[‡]	1.70±1.40[‡]	4.59	0.00[*]
n-3 fatty acids, g	0.48±0.45	0.18±0.20	4.39	0.00[*]	0.37±0.36[‡]	0.15±0.14[‡]	3.55	0.00[*]
n-6/n-3	11.9±7.78	18.0±26.5	-1.38	0.18				
Carbohydrate, g	158±67.4	168±48.0	-0.95	0.35	68.4±15.0[‡]	77.6±37.9[‡]	-1.52	0.14
Dietary fiber, g	9.24±6.30	7.22±4.06	1.82	0.08				
Ca, mg	414±242	365±159	1.22	0.23	87.0±55.6	74.4±46.4	1.55	0.13
P, mg	565±321	540±168	0.48	0.63	112±53.1	106±33.8	0.65	0.52
Fe, mg	6.78±2.89	8.16±3.40	-1.94	0.06	98.8±44.0	117±44.9	-1.70	0.10
Na, mg	1,880±1,205	1,382±820	3.30	0.00[*]	220±112	159±76.3	3.55	0.00[*]
K, mg	1,601±741	1,448±468	1.10	0.28	90.6±31.3	84.5±48.2	0.59	0.56
Zn, mg	5.27±2.16	5.78±2.71	-1.15	0.26	145±58.0	153±55.8	-0.75	0.46
Vit A, μgRE	412±218	430±363	-0.25[§]	0.80	119±60.5	123±111	-0.21[§]	0.84
Vit B1, mg	0.66±0.34	0.62±0.20	0.59	0.56	132±60.4	119±51.8	0.89	0.38
Vit B2, mg	0.72±0.39	0.69±0.23	0.35	0.73	120±64.3	113±46.4	0.56	0.58
Vit B6, mg	1.11±0.66	1.11±0.47	-0.01	1.00	172±84.0	181±93.8	-0.40	0.69
Niacin, mg	8.13±3.77	9.40±4.00	-1.52	0.14	134±61.5	159±117	-1.17	0.25
Vit C, mg	110±74.1	93.9±71.0	0.99	0.33	244±181	209±179	0.97	0.34
Folate, mg	136±73.2	149±60.4	-0.68	0.50	84.1±44.1	97.9±57.2	-1.02	0.32
Vit E, mg	8.75±4.60	6.93±3.04	2.22	0.03[*]	156±65.1	123±53.9	2.22	0.03[*]
Cholesterol, mg	132±111	151±182	-0.63	0.54				
Vit D, μg	3.09±3.89	4.64±4.12	-1.89[§]	0.06	61.8±77.8	92.9±82.5	-1.89[§]	0.06

%KDRIs: percent ratio of energy and nutrients to the recommended intake in the 2010 Dietary Reference Intakes for Koreans; Vit: vitamin.
Data are presented as mean±standard deviation.
[†]% estimated energy requirement.
[‡]% energy from the presented nutrient.
[§]Wilcoxon's matched-pairs signed-ranks test for non-normally distributed data.
[*], [**]Significant correlation between before and after intervention by paired t-test except non-normally distributed data ([*]$p<0.05$ and [**]$p<0.01$).

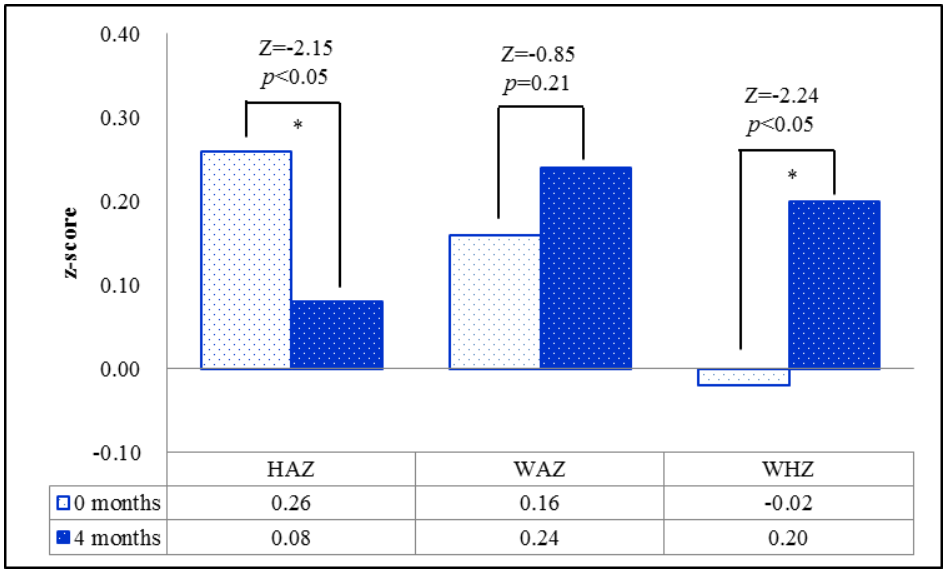

Figure 1. Changes in the z-scores before and after 4 months of nutrition intervention for children with atopic dermatitis. Significant differences in z-scores between before and after 4 months of nutrition intervention are denoted by $^{*}p<0.05$, as assessed by Wilcoxon's matched-pairs signed-ranks test for non-normally distributed data. HAZ: z-score of height for age; WAZ: z-score of weight for age; WHZ: z-score of weight for height.

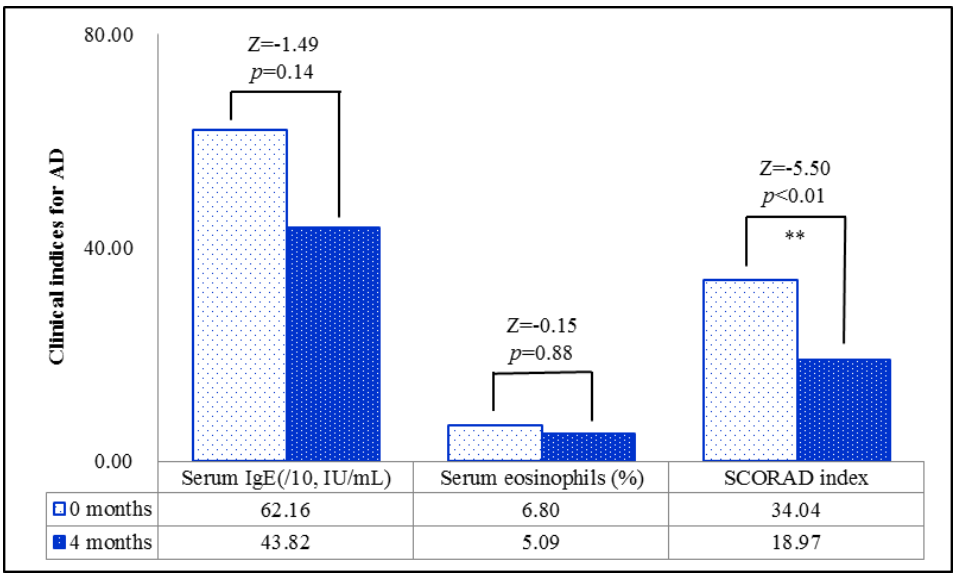

Figure 2. Changes in the three clinical indices before and after 4 months of nutrition intervention for children with atopic dermatitis. Significant difference in the three clinical indices for the severity of atopic dermatitis between before and after 4 months of nutrition intervention is denoted by $^{**}p<0.01$, as assessed by Wilcoxon's matched-pairs signed-ranks test for non-normally distributed data. The units of measurement for serum IgE and serum eosinophils were IU/mL and % total leukocytes, respectively. Data for serum IgE were divided by 10 because of the excessively high values comparing with others. AD: atopic dermatitis, IgE: immunoglobulin E, SCORAD: SCORing of Atopic Dermatitis.

predictive decision points, indicating unnecessary food elimination. Moreover, this also suggests that timely and reliable nutrition intervention may be required in these children.

In agreement with previous studies indicating a maternal, rather than paternal, connection with the occurrence of AD,[36,37] a maternal history of allergic disease, including AD, was found to be more highly associated with severe AD than paternal history in this study. A significant association between maternal stress derived from guilty conscience or difficulties from caring for the AD-affected child and the severity of the child's AD has been reported,[38] likely owing to the fact that these mothers are more likely to use unfounded therapies for AD, such as excessive food restriction. Such behaviours might induce unnecessary elimination or limited intake of foods that supply the majority of vital nutrients needed for the child's active growth, such as eggs, milk, or different protein sources. Because children on elimination diets might be at nutritional risk, especially when they have more than one food allergen, comprehensive and individualized nutrition intervention should be executed as a means for not only teaching the children and parents how to avoid specific foods identified as an allergen, but also

for providing guidance on how to appropriately replenish nutrients prone to deficiency due to elimination. In addition, close attention should be paid to breast milk feeding. Although the effects of breast milk and maternal diet on the development or severity of AD in children is a disputed issue, a previous study showed that hydrolyzed formula substantially reduced the incidence of AD in high-risk infants,[39] whereas exclusive breastfeeding for 4 months was found to be associated with an increased risk of AD in children with no parents with allergies in another study.[40] If an infant fed with breast milk had higher food-specific IgE levels for milk than the food allergy decision point,[27] recommendations such as the control of mother's food intake or the change to hydrolyzed formula feeding requested in this study would be worth consideration.

The effects of dietary factors such as essential PUFAs and antioxidant vitamins on the severity of AD have been covered in several studies, with the intake or supplement of essential PUFAs (n-6 and n-3),[41,42] vitamin D,[43,44] vitamin E,[45] and zinc[46] having been reported as beneficial for decreasing the severity of AD, while vitamin A[47] and vitamin C[20] have been shown to be associated with improvements in asthma rather than in AD. The effects of PUFAs on AD have been suggested as promotion of atopic sensitization and inflammation upon increasing and decreasing dietary intakes of n-6 and n-3 PUFAs, respectively.[48] Linoleic acid (n-6), the most common dietary PUFA, is converted into arachidonic acid, which is metabolized by cyclooxygenase and lipoxygenase, and is ultimately used to produce 2-series prostaglandins, thromboxanes, and 4-series leukotrienes, which are proinflammatory lipoxins affiliated with asthma and atopic disease. Conversely, n-3 PUFAs, including eicosapentaenoic acid, compete with arachidonic acid as a substrate for cyclooxygenase and lipoxygenase and may decrease the synthesis of proinflammatory prostaglandins and leukotrienes.[49] Further, antioxidants may prevent the free radical-induced chain reactions that otherwise lead to lipid peroxidation and damage to the cell membranes or DNA, both of which may be involved in the pathogenesis of allergic disease.[50,51] Accordingly, our result that the n-6 and n-3 PUFA intake levels before intervention in children with moderate severity of AD, whose mean SCORAD index was between 25 and 50,[25,52] were under the recommended intake level of the KDRIs could be interpreted similarly. In addition, we found that the n-6 and n-3 PUFA, and vitamin E intakes showed significant negative correlations with the total serum IgE level; this may indicate the possibility that children with AD might be improved through supplementation or increases in the intakes of foods rich in these nutrients.

Although some previous studies have reported that the calcium intake in children with AD was lower than that in children without AD[53] and that some subjects with AD displayed calcium intake less than the RNI,[54] the calcium intake of the children in our study almost met the RNI of the KDRIs (93.8±67.3 %KDRIs). However, the negative correlation observed between calcium intake and the SCORAD index corresponds with the previous findings that the calcium intake is lower in subjects with AD. The reason for this observation could be speculated to be the fact that dairy foods, the major source of calcium, are commonly restricted in children with FA, especially in children with severe AD. However, the possibility of dairy food as the causative allergen appears to decline with age, and continuous assessment and nutrition recommendations modified according to the allergen status should be performed. Contrary to calcium, a positive association between folate intake and the SCORAD index was observed herein, and this finding might be explained by the fact that high folate-containing foods, such as mostly fruits and vegetables, are consumed in larger amounts as an alternative to the restricted foods in children with more severe AD, as they are usually unlikely to act as sensitized allergens. Furthermore, unlike the results shown in some previous studies, the zinc intake was found to positively correlate with the percent of serum eosinophils. Although further studies for precise interpretation are necessary, it might, nonetheless, be supposed that copper deficiency induced by excessive zinc intake would have resulted in increased serum eosinophil levels and changes in the white blood cell distribution.[55]

With regard to AD, the effects of nutrition intervention on the manifestation and severity of AD have been assessed in several studies. Kim et al[19] reported that 12-week medical nutrition therapy comprising of general dietary therapy, intake of balanced meals, and emphasis on n-3 PUFA contents in the foods for AD patients resulted in the subjects' dietary qualities improving and in significant decreases of the serum IgE and interleukin-4 levels. Rokaitė et al[56] also demonstrated that one-year diet treatment with individualized balanced replacement diets for children with AD helped to control their nutrition status and showed a positive effect on the clinical course of AD. Taken together, these findings suggest that the desirable nutrition intervention for people with AD should consist of two main approaches: elimination or reduction of the causative foods or nutrients with adequate alternatives, and supplementation of nutrients with protective effects on the progress of AD.

The five sessions of individualized nutrition intervention implemented in our study, which contained five common themes, significantly improved the growth status of the study subjects, as indicated by the WHZ; reduced the severity of AD, as expressed by the SCORAD index; and tended to be associated with a lack of severely deficient nutrients. The decrease in HAZ was unexpected, and we speculate that the calcium intake of the subjects may be one possible explanation for this finding. Calcium, mostly supplied from dairy foods and some fish, is an essential nutrient for bone growth and increases in height. Children who were confirmed to have the sensitized allergen to milk or certain kinds of fish through the oral food challenge were prohibited from consuming these foods to prevent exacerbation of the AD. Further, as not only the calcium level, but also the n-6, n-3 PUFAs and vitamin E intakes may decline after such an intervention, the decreased percent of energy from lipids and the elimination of fish or nuts containing high levels of n-3 PUFAs are important issues. The treatment or improvement of AD is often the first goal of treatment, and complete elimination of foods may thus be considered more important than improving the growth status or nutritional balance in the acute setting. However, in the long-term setting, the

appropriate intakes of calcium, essential PUFAs, and vitamin E by nutrition intervention combined with useful food preparations and tips will be more helpful for the control of AD-related symptoms and nutrient intake balance. Of note, the vitamin D and iron intakes displayed increasing trends without significance after the intervention in this study, in spite of the small spectra of food choices, and their intake levels after prolonged intervention should be further assessed to validate the effects on these nutrients.

There were some limitations in our study. First, all children in our study had AD with FA, and comparison with a control group to verify the effects of individualized nutrition intervention could not be implemented. The study subjects were all patients who visited a hospital for the treatment of AD, and it would not have been ethical to form a control group not given nutrition intervention. Second, though the children's diets were checked by diet records and were individually modified at every intervention session, they were treated as outpatients, and their food intake could hence not be controlled completely. Furthermore, other adjuvant therapies such as bathing and skin emollients without steroidal ingredients were allowed, and may have affected the results. Third, the drop-out rate was high, with 42 children (54.5%) failing to complete all intervention session. This was higher than the expected 20% of drop-out rate, and might have caused a decrease in the overall power of this study, even though clinical improvement, as expressed by the reduction of the mean SCORAD index, was observed. Finally, the last two limitations were that the included patients had a wide age span, ranging from 0.34 to 15.9 years, and that the study period (4 months) might have been too short to show definite changes in the nutritional parameters evaluated using z-scores, especially in patients in mid-to-late adolescence (>13 years), when the rapid growth phase has passed. However, in this study, it was impossible to confirm the effects of the short study period in this particular population, as only 1 out of the 35 patients who completed 4 months of nutrition intervention was in mid-to-late adolescence. Nonetheless, to evaluate the changes in nutritional parameters in the future, the age range of the subjects might need to be considered.

This study also has several strengths. Importantly, the results of this study were obtained from both traverse and longitudinal researches, and the characteristics at specific time points along with their changes over time were examined together. These findings can be used as a basis for further research in the future. Moreover, our nutrition intervention was conducted in an individualized manner, with five common major themes tailored according to the disease and nutrition status of each patient. Lastly, as the subjects in this study were mainly moderate AD patients, the results could potentially be broadly applied to children with both mild and moderate AD.

In conclusion, in this study, we analyzed 1) the characteristics and nutrient intake status, 2) the correlations between various characteristics and nutrient intakes, and 3) the effects of individualized nutrition intervention on the severity of AD and nutrient intake status in pediatric AD patients with FA. The findings of this study may be used as a basis for planning comprehensive nutrition interventions as a means to supply proper alternatives to restricted foods in order to prevent malnutrition and poor growth in children with AD and FA, and to improve the severity of AD. Further studies examining each subject's needs in detail and with prolonged implementation periods of the intervention are required to determine the accurate correlations between the clinical indices for the assessment of AD status and nutrient intakes, and studies aimed at comparing the differences between intervention and control groups after individualized nutrition intervention are warranted to further clarify its effectiveness.

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AUTHOR DISCLOSURES

None of the authors have a conflict of interest.

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Original Article

Children with atopic dermatitis in Daejeon, Korea: individualized nutrition intervention for disease severity and nutritional status

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韩国大田特应性皮炎患儿：个体化营养干预对疾病严重程度和营养状况的影响

背景与目的：特应性皮炎是小儿最常见的慢性炎症性皮肤病之一，某些食物过敏原和营养素与特应性皮炎的发展和严重程度密切相关。而避免致病的食物被认为是主要的治疗方案，未经证实的过度限制会引起不必要的食物摄入受限，从而导致营养缺乏，发育不良。本研究旨在确定特应性皮炎患儿的特点和营养摄入状况，探讨个体化营养干预的效果。**方法与研究设计：**我们回顾性分析了接受 4 个月个性化营养干预与排除膳食限制的 77 例特应性皮炎患儿的电子医疗记录。检查患者临床特征、营养素摄入状况以及干预前后的临床状态。**结果：**干预前，5 名儿童体重身高 Z 评分低于-2.0，48.1%的患儿有食物受限；这些患儿的 SCORAD 指数显著高于没有特应性皮炎的儿童，干预前，限制食品的数量与疾病严重程度呈正相关。n-6 和 n-3 脂肪酸、钙、叶酸和维生素 D 的摄入量均低于韩国人的推荐摄入量。干预后，35 名患儿相对身高体重 Z 评分显著增加，SCORAD 指数显著降低（$p<0.05$）。**结论：**个性化营养干预通过改善营养素摄入，似乎有助于缓解特应性皮炎的严重程度，改善生长状态。

关键词：特应性皮炎、个体化营养干预、SCORAD 指数、生长、营养状况