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Original Article

Prebiotic supplementation modulates serum immunoglobulin E levels and improves total SCORing atopic dermatitis score in children with atopic dermatitis: a randomized double blind controlled trial

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Article History
Received:
08/02/2015
Revised:
15/03/2015
Accepted:
30/03/2015

Keywords:
Atopic dermatitis,
Immunoglobulin E,
Prebiotics,
Fructooligosaccharid/inulin

A B S T R A C T

Background: Atopic dermatitis (AD) is a prevalent chronic disease in children aging from 6 months to 12 years old. Recent studies have shown a positive effect of prebiotics in the prevention and treatment of AD. The mechanism of this effect has not been clearly established. The objective of this study was to investigate the effect of supplementation of prebiotic on serum immunoglobulin E (IgE) levels and total SCORing AD (SCORAD) score in 7-24 months old children with AD.

Methods: A total of 70 children with AD in a double-blind controlled clinical trial were randomly divided into two groups. For 3 months, the treated group received prebiotic (inulin + fructooligosaccharide), and the control group received placebo (dextrin powder). At the beginning and at the end of the intervention, the SCORAD test questionnaire was completed for all children by a physician and serum levels of IgE were determined. The collected data were analyzed by SPSS Ver. 18 software, using independent and paired t-tests and regression analysis. A $p < 0.050$ was considered statistically significant.

Results: The total SCORAD score and serum IgE levels before intervention were similar in the treated and control groups, and no correlation was found between these variables. The intervention resulted in a significant improvement in the total SCORAD score in the treatment group compared to control group ($p < 0.001$). Moreover, prebiotic supplementation resulted in significant decrease in serum IgE levels in the treated compared to control group ($p < 0.001$). A significant positive correlation was found between total SCORAD score and serum IgE levels in the intervention group ($r^2 = 0.20$; $p < 0.001$).

Conclusion: Prebiotic supplementation may have beneficial effects on serum IgE, which may improve SCORAD. Our findings suggest prebiotic consumption as an adjuvant treatment of dermatitis.

Citation: Ghanei N, Siassi F, Zandieh F. **Prebiotic supplementation modulates serum immunoglobulin E levels and improves total SCORing atopic dermatitis score in children with atopic dermatitis: a randomized double blind controlled trial**. J Nutr Sci & Diet 2015; 1(2): 80-5.

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Introduction

Atopic dermatitis (AD) is a chronic recurrent disease during infancy [1]. It is also seen in children and adults [1]. 10-20% of children in

the world suffer from AD [1]. 50% of the children show the symptoms during the 1st year after birth and 30% during the ages of 1-5 [2]. During the past 30 years, the outbreak of this disease has been increasing, probably due to the changes in lifestyle and limited exposure to infectious agents during the 1st year of life [3, 4]. There are strong evidences for an involvement of gut microbiota in the promotion of immunity after birth [5]. The immune system of a newly born atopic or non-atopic baby is in favor of T-helper cells2 (Th2) responses [6, 7]. However, environmental stimulation of the immune system in healthy children by gut microbiota, such as *Bifidobacterium*, promotes the balance ratio in favor of Th1 reactions [7, 8]. It is suggested that the delayed maturation in AD children shifts the ratio of Th1/Th2 toward Th2 and increases the levels of related cytokines (interleukin [IL-4]) and immunoglobulin E (IgE) [6, 9].

Prebiotics are indigestible food substances that selectively stimulate the growth of selected nonpathogenic beneficial bacteria of the gastrointestinal tract [10]. Various prebiotics, such as fructooligosaccharides (FOS) and galactooligosaccharides (GOS) stimulate the growth of intestinal probiotics such as *Bifidobacteria and Lactobacillus rhamnosus* [11, 12]. Therefore, administration of prebiotics to AD children might shift the ratio of Th in favor of Th1, and hence contribute to the treatment of these patients. We previously showed that FOS+inulin supplementation to the 7-24 months old children for 3 months reduces total SCORD by more than 90%. In this investigation, we report the probable mechanism of this reduction [13]. Thus, the objective of the present study was to investigate the effect of supplementation of prebiotic on serum IgE levels and total SCORing AD (SCORAD) score in 7-24 months old children with AD.

Methods

Patients and study design

The detailed study design was reported previously [13]. In short, 90 AD children aged between 7 and 24 months (new cases) in a double-blind placebo-controlled clinical trial, were consecutively enrolled in two parallel groups, assigned at random to prebiotic and placebo groups after obtaining written consent from their parents. AD diagnosis was made by the physician according to the standardized criteria [14]. The inclusion criteria for the trial were: full term AD child aged 7-24 months old; delivered by cesarean section with birth weight appropriate for gestational age and exclusively breast or milk-fed up to 6 months of age. All children with the acquired immunosuppressive disease, or any other kind of chronic diseases, or receiving any systemic corticosteroid or other immunosuppressive drugs during the 3 months prior to the study were excluded. All patients enrolled in the study had the consent of the parents as well informed, cooperative participants in the study.

Exclusion criteria during the trial were: consuming prebiotics supplements or placebo < 75 days during the 90 days of intervention; showing any side effects due to the consumption of the prebiotics or placebo; and receiving any systemic corticosteroid or other immunosuppressive drugs.

The prebiotic powder preparation contained 50% inulin and 50% FOS (Nestle, Iran). The placebo powder contained maltodextrin. The 7-12, 13-18 and 19-24 months old children consumed approximately 5, 7.5 and 10 g of prebiotic or placebo per day for 90 days, respectively. The daily dose was calculated as 0.8 g of the prebiotic or placebo mixture per 100 ml of milk, after approximating the amount of milk consumed by the children according to their age and weight. Consumption of any probiotic or prebiotic food supplements were prohibited during the intervention period.

The prebiotic and placebo supplements were similarly packed and were given to the parents for 1-month consumption only, and the amounts consumed were recorded in a monthly visit during the 3 months of the study. During the study period, the standard AD treatments remained unchanged, all patients applied emollients, and some of them used topical corticosteroids or topical immunosuppressive for a short time period during the intervention. A volume of 5 ml non-fasting blood sample was collected from the samples at the beginning and at the end of the trial. Blood samples were centrifuged at 3000 rpm for 10 minutes and serum samples were analyzed by ELISA to determine the level of IgE in serum.

The study protocol was approved by the Ethics Committee of Tehran University of Medical Sciences in accordance with the Helsinki Declaration and the guideline of Iranian Ministry of Health and Medical Education and registered in IRCT (138809072779N1).

Evaluation

The parents, their children, the dermatologist

and the responsible technician analyzing the data were blinded to the children's supplementation. Clinical examination included body weight and height measurements, and SCORAD. Standardized 24-hour dietary recall questionnaires were also completed at the beginning and at 1, 2 and 3 months after the intervention. Each patient was examined by the same dermatologist at each visit. The standardized SCORAD scoring system developed by the European Task Force for AD [15] combines the clinical evaluation of intensity and extent, with subjective itch and insomnia score indicated by parents on a visual analog scale. The objective SCORAD ranges from 0 to 83. When the added subjective score, then the total SCORAD score extends to a maximum of 103.

Other information such as the birth data from the birth records and feeding practices were obtained directly from the mothers.

Statistical analysis

All data were expressed either as an absolute value, percent or mean ± standard deviation. Chi-square and Fisher exact tests were performed for the relationship between the qualitative data. Independent and paired t-tests were used to test the differences between the means and correlation between serum IgE levels with total SCORAD was estimated by regression analysis. A $p < 0.050$ was considered statistically significant. All data were analyzed using SPSS software ver.17 (SPSS Inc., Chicago, IL, USA).

Results

Of the 90 patients included in the study, 70 patients completed the trial. The reason for not completing the trial was because of non-attendance to scheduled visits (10 patients), lack of interest of parents to continue the program (9 patients), and diarrhea (1 patient).

There was no significant difference between the prebiotic and placebo fed groups regarding to qualitative and quantitative variables before and after the interventions (Tables 1 and 2). There was no significant difference between the two groups regarding the mean daily intake of vitamins A, E, C, dietary fiber and milk (any type) before and after interventions (Table 3).

There were no significant differences between the two groups considering the means of serum IgE levels and total SCORAD scores before the intervention (Table 4). After the intervention, the differences between the two groups as well as in each group before and after the intervention were highly significant (Table 4). Furthermore, a significant positive correlation was found between the total SCORAD scores and serum IgE levels after treatment in the intervention group ($r^2 = 0.20$; $p < 0.001$).

Discussion

We hypothesized that using prebiotic as a supplement with common topical treatment in AD, could give better results in treating AD patients than topical treatment alone. The findings of this study indicated that after using prebiotic for 3 months the serum IgE levels ($p < 0.005$) and total SCORAD score ($p < 0.001$) were significantly decreased in both groups compared to before treatment. However, the total SCORAD score after the treatment were most significantly decreased in the treated group as compared to the placebo group ($p < 0.001$). There were no significant differences between the two groups before the intervention (Table 4). Most probably this reduction was due to consuming prebiotics since all known confounding factors (such as type of delivery, parent's age during pregnancy, consumption of antibiotic, consumption of nutritional supplement and intake of some nutrients such as vitamin A, C, E, fiber,…) were similar between the two groups at the beginning of intervention and were controlled during the study (Tables 1-3). The recovery was observed in both groups after 3 months due to the similar usage of skin care and other similar care such as bathing, etc.

A previous study has shown that consumption of prebiotic supplement (mixture of GOS/FOS) with hypo-allergen formula during the first 6 months of life by infants at high risk of atopic reduces the incidence of AD [16].

Table 1. Quantitate characteristics of the study groups

Characteristics	Intervention n = 35 Mean ± SD	Control n = 35 Mean ± SD	p value
Mother's age during pregnancy (years)	27 ± 5.0	26.7 ± 5.0	0.760
Weight at birth (g)	3300 ± 337	3149 ± 391	0.080
Length at birth (cm)	50.9 ± 3.9	50.6 ± 2.7	0.760
Head circumference at birth (cm)	34.7 ± 1.0	34.1 ± 1.6	0.095
Age (month)	17.6 ± 7.4	14.9 ± 6.3	0.100

SD= Standard deviation

Table 2. Qualitative characteristics of the study groups

Characteristics	Intervention n = 35 n (%)	Control n = 35 n (%)	Total n = 70 n (%)
Sex			
Girl	13 (18.6)	17 (24.3)	30 (42.9)
Boy	22 (31.4)	18 (25.7)	40 (57.1)
Birth order			
First	19 (27.1)	22 (31.4)	41 (58.6)
Other	16 (22.9)	13 (18.6)	29 (41.4)
Place of residence			
Town	25 (35.7)	28 (40)	53 (75.7)
Village	10 (14.3)	7 (10)	17 (24.3)
History of allergy			
Yes	15 (21.4)	23 (32.9)	38 (54.3)
No	20 (28.6)	12 (17.1)	32 (45.7)
Family history of allergy			
Yes	30 (42.9)	32 (45.7)	62 (88.6)
No	5 (7.1)	3 (4.3)	8 (11.4)
Type of consuming milk			
0-6 month breast	29 (41.4)	27 (38.6)	56 (80)
Other	6 (8.6)	8 (11.4)	14 (20)
Type of consuming milk during intervention			
Breast	9 (12.9)	11 (15.7)	20 (28.6)
Other	26 (37.1)	24 (34.3)	50 (71.4)
Type of ointment during intervention			
Emollient	13 (18.6)	12 (17.1)	25 (35.7)
Corticosteroid	13 (18.6)	17 (24.3)	30 (42.9)
Corticosteroid+immunosuppressive	9 (12.9)	6 (8.6)	15 (21.4)
Consumption of antibiotic during intervention			
Yes	14 (20)	7 (10)	21 (30)
No	21 (30)	28 (40)	49 (70)
Consumption of supplements during intervention			
Yes	19 (27.1)	21 (30)	40 (57.1)
No	16 (22.9)	14 (20)	30 (42.9)
History of disease during intervention (common cold, constipation, diarrhea)			
Yes	10 (14.3)	9 (12.9)	19 (27.1)
No	25 (35.7)	26 (37.1)	51 (72.9)

Table 3. Mean daily intake of nutrients, fiber and milk of the study groups

Variables	Intervention n = 35			Control n = 35			p value
	B	A	D	B	A	D	
Vitamin E (mg)	5. 1	4.2	0.9	5	4.8	0.2	0.320
Vitamin C (mg)	71	75	-4	71.4	76.1	-4.7	0.810
Vitamin A (µg)	590	576	14	550	537	13	0.900
Selenium (µg)	23.6	23.7	-0.1	23.1	23.8	-0.7	0.060
Fiber (g)	8.9	10.7	-1.8	8.39	10.6	-2.2	0.070
Milk (ml)	1250	1313	-63	1260	1320	-60	0.900

B = Before intervention; A = After intervention; D = Difference

Table 4. Serum IgE levels and total SCORAD scores of the study groups

Variables	Intervention n = 35 Mean ± SD	Control n = 35 Mean ± SD	p value
Serum IgE (IU/ml)			
Before	160 ± 73	158 ± 40	0.340
After	107 ± 43	93 ± 56	0.001
p value	< 0.005	< 0.005	
Total SCORAD			
Before	53.9 ± 23.6	43.4 ± 20.9	0.062
After	4.3 ± 9.6	19.4 ± 13.0	0.001
p value	< 0.001	< 0.001	

SCORAD = SCORing atopic dermatitis; IgE = Immunoglobulin E

The stools of a sub-group, of these children were analyzed for Bifidobacters. The numbers of Bifidobacters were significantly increased in the children receiving prebiotic with no significant changes in the numbers of Lactobacillus. The stools of the children were not analyzed in our study. However, we can assume that prebiotic supplementation in our study may have also caused an increase in the numbers of Bifidobacters in the guts of the children, and thus promoted the balance ratio of Th1/Th2 toward Th1, resulting in a reduction of SCORAD score. Contrary to this assumption is the recent study carried out by Shibata et al. in AD infants and children < 3 years of age [17]. They treated AD infants with 1 g of prebiotic (Kestoz type) and older children with 2 g for 3 months and found no significant relationship between SCORAD score improvement and the increase of the number of Bifidobacters in the stool. Therefore, we have to assume that other mechanisms are also involved in shifting the balance of Th1/Th2 towards Th1.

In another study, Passeron et al. treated moderate to severe 2-12 years old AD children with either prebiotic or prebiotic plus synbiotics for 3 months. The intensity of AD decreased almost to the same extend in both groups, and no significant differences were observed between the two groups; i.e., adding synbiotics had no advantage over the prebiotic alone [9]. The reduction of the total SCORAD score in their study was less than our study, indicating that treating AD children with prebiotic at earlier age might be more efficient than later in life.

It is worth mentioning that prebiotic and probiotic might have also preventive capacity to reduce allergy in at risk children as indicated by the study of Kukkonen et al. [18]. High risk pregnant women treated with both prebiotic and probiotic 2-4 weeks before delivery and the infants up to 6 months of age resulted in a reduction of IgE-associated atopic diseases in these children at 2 years of age. They also found an inverse association between atopic diseases and colonization of the gut by probiotics.

About 70-80% of AD patients have a higher serum IgE level [19]. When IgE binds to the surface of mast cell stimulates releasing the cytokines such as tumor necrosis factor-α, that would be suppressed the Th1 cytokines [20]. In 345 children with AD the significant relation between serum IgE level and the severity of SCORAD was seen [21]. Also in another study was conducted in 20 children with AD significant relationship between serum IgE and IL-18 levels and total SCORAD score was determined. However, there was no significant difference in respect of serum levels of IL-12/p40 between patients and control group [20].

Conclusion

Our study showed that treating AD children with prebiotic reduces the total SCORAD score and serum IgE levels. Further studies are needed to clarify the mechanism of prebiotic impact on AD reduction in children such as the shift of the ratio of Th1/Th2 toward Th1 and IL4 changes.

Acknowledgments

The authors wish to thank Under Secretory of Research, Tehran University of Medical Sciences for the financial support and Nestle (Iran) for providing prebiotic and all the children participating in this study.

Conflict of interest

None of the authors had any personal or financial conflicts of interest.

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