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Synbiotics could not Reduce the Scoring of Childhood Atopic Dermatitis (SCORAD): A Randomized Double Blind Placebo-Controlled Trial

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ABSTRACT

Despite preliminary evidence, the role of probiotic and synbiotic in treatment of the atopic dermatitis has shown varying results. We aimed to evaluate whether synbiotic supplementation decrease severity of atopic dermatitis (AD) in childhood. In a randomized double blind-placebo controlled trial, we evaluated the synbiotic supplementation efficiency on the treatment of atopic dermatitis.

Infants aged 1–36 months with moderate to severe atopic dermatitis were randomized (n=41) and received either synbiotic (probiotic plus prebiotic) (n=20) or placebo (n=21) daily as a powder for two months. Emollient (Eucerin) and topical corticosteroid (Hydrocortisone) were permitted.

Children were scored for severity of atopic dermatitis (SCORAD). Also allergen Skin Prick Tests (SPT), IgE blood level and eosinophil count were measured at first visit. Patients' SCORAD were reevaluated at the end of intervention. We followed 36 out of 41 subjects for two months (drop out rate = 9%).

In the whole group, the mean Total SCORAD (at base line 40.93) decreased by 56% ($p=0.00$). The mean Objective SCORAD (at base line 31.29) decreased by 53% ($p=0.00$). There was no significant difference in the mean decrease of total SCORAD between placebo (22.3) and synbiotic groups (24.2). There was also no difference between two intervention groups in the mean decrease of total SCORAD regarding to different demographic, clinical and para clinical subgroups.

This study could not confirm synbiotic as an effective treatment for childhood atopic dermatitis and further studies are needed. These findings challenge the role of synbiotics in the treatment of childhood atopic dermatitis.

Key words: Atopy; Dermatitis; Infants; Prebiotics

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INTRODUCTION

Atopic dermatitis (AD) is a chronic itchy inflammatory disease of the skin, which more than 2,500 years ago Hippocrates described it. AD is the most common chronic skin disease in childhood which affects 10-20% of children worldwide.¹⁻³ Atopic dermatitis has a major impact on the quality of life of patients and their families.⁴ AD is recognized as the earliest presentation of allergy and Infants with AD are prone to asthma and allergic rhinitis later in the childhood.^{5,6}

The prevalence of atopic dermatitis and other allergic diseases have increased in recent decades.⁷ Many studies have suggested that environmental factors may be the major trigger factors in the development of allergic disorders.⁸ While several environmental exposures are thought to be involved, lack of microbial exposures during infancy is known as immune system deviation towards the development of allergic disorders.⁹ It is assumed that the increasing incidence of allergic disorders in developed countries is connected to improvement in hygiene and decreased exposure of the immature immune system to microbes in early childhood. This has become known as the hygiene hypothesis which first, suggested by Strachan in 1989.¹⁰ Strachan suggested that the decreased number of infections cause a greater risk of allergy. The hygiene hypothesis was supported by the idea of postnatal immune deviation which presents a biologically acceptable mechanism. According to this theory, at birth, the human immune system has more noticeable Th2 than Th1 components and exposure to infections in early childhood induce a gradual shift toward greater Th1 responses and a 'normal immune response balance'.¹¹⁻¹³ The intestinal microbial flora is the major source of microbial exposure, consisting of 10^{14} microorganisms and may be a contributor to allergic disease due to its profound effect on mucosal immunity.¹⁴ Microbial colonization of the gastrointestinal system is related to lifestyle and geographic factors that may be an important factor for the heterogeneity in disease incidence in the world.¹⁵ There are differences in the composition of the gut micro flora between infants living in countries with a different prevalence of allergy and between healthy infants and infants with allergy.¹⁶⁻¹⁹ Because allergic immune responses manifest in early life, there has been obvious interest in the potential benefits of modifying

the gastrointestinal flora by using probiotic and prebiotics supplementation. Probiotics are specified as live microorganisms which, when prescribed in adequate amounts, confer a health benefit on the host.²⁰ Prebiotics are defined as non-digestible oligosaccharides, such as fructo-oligosaccharides that selectively stimulate the growth of Bifidobacteria and Lactobacilli.²⁰ Synbiotic is a term which is defined as mixture of prebiotics and probiotics.²⁰ Probiotics opened new therapeutic window for management of atopic diseases.²¹⁻²⁴ Now there is good evidence, that specific strains of Lactobacilli and Bifidobacteria can influence immune system through different ways including influence on enterocytes, antigen presenting cells, regulatory T cells, and effectors T and B cells. According to immunologic studies, probiotics would be useful in early childhood, when immune system is still developing. Considering the prevalence of atopic dermatitis and its immuno pathogenesis, it would be logical to use probiotics and prebiotics for prevention and treatment of AD which probably prevent other allergic diseases which progress later. Therefore we planned a randomized double blind placebo control study to evaluate the effect of synbiotics in treatment of atopic dermatitis in Iranian children.

PATIENTS AND METHODS

Study Design

We used a double-blind, randomized, placebo-controlled trial to investigate the effects of synbiotic supplementation on the treatment of atopic dermatitis in childhood. The patients were visited in a referral allergy clinic in the Children Medical Center Hospital of Tehran University of Medical Sciences, Tehran, Iran, from December 2008 until November 2009. Patients allocated randomly to receive either synbiotic or placebo daily for two months. Randomization was performed according to a computer-generated balanced block randomization to synbiotic and placebo groups. At enrollment, we assigned the study number and provided the participants with the appropriate sachet. All study investigators and participants were blind to treatment assignment during the study. The synbiotic and placebo supplements were image-matched and identical in appearance, taste and smell. In the synbiotic group, children took daily one sachet containing 10 milligram mixture of 1×10^9 CFU/ of seven strain probiotics plus prebiotic (990 milligram fructo-

oligosaccharides). In the placebo group, children took daily one sachet containing 1000 milligram sucrose. The synbiotic and Placebo sachets were supplied by Probiotics International Ltd (UK). The sachet powder was mixed with water, breast milk, formula or solid food was given once daily. Treatment was generally well tolerated in both groups and no serious side-effects were observed. We instructed usual treatment of atopic dermatitis including bathing habits, moisturizing cream (Eucerin) and topical corticosteroid (Hydrocortisone 1%) similarly for both groups. None of the patient changed diet during the study period. Children were randomized to receive one of the synbiotics or placebo daily, which continued for as long as 2 months.

All study aspects of the protocol were approved by the Ethics committee of Immunology, Asthma and Allergy Research Institute (IAARI). Written informed consent was obtained from all parents. Throughout the study, both participants and investigators remained blind to the treatment groups. All analysis was made by a statistician with knowledge only of groups. After all analysis had been made the code was broken.

Participants

We recruited children aged 1–36 months with Atopic Dermatitis. Patients With moderate to severe AD (SCORAD>25) were included to study. Following giving information to parents about study, the parents were invited to let their children participate in the study. Infants' demographic, clinical characteristics and SCORAD Index were collected by a fellow of allergy at first visit and final visit 2 month later (Table 1). Infants were treated for an average of 59 days in the synbiotic group and 58 days in the placebo group. Exclusion criteria were age less than 1 month and more than 36 months, SCORAD<25, recurrent infections(as an evidence of immunodeficiency), congenital abnormality, chronic disease and problem in eating and administration of systemic corticosteroids.

Clinical Assessments

At enrolment all parents answered a questionnaire about demographic data and medical history such as age; sex; family history of allergic disease; weight at birth; family size. Also information about factors that could influence the effect of synbiotic on AD such as vaccination, hospitalization, antibiotics consumption, day care attendance, diet, and having pet at home were collected. Children's eczema was diagnosed by

typical features and according to Hanifin and Rajka criteria. Eczema severity was assessed using Scoring Atopic Dermatitis index (SCORAD).²⁵ The Objective SCORAD was calculated by the clinical evaluation of intensity and extent of the eczema. By adding subjective symptom of pruritus and sleep loss (which was indicated by parents) to Objective SCORAD, the Total SCORAD was calculated. The infants were evaluated for above data and SCORAD index at baseline and two months later by a fellow of allergy. Patients were visited every two weeks and followed for two months. Venous blood samples were drawn from consenting subjects (one milliliter EDTA and one milliliter clotted blood) at first visit. Total IgE antibody level was coalutated by ELISA kit (from Genesis Diagnostics Ltd. Combrigheshire, U.K) and complete blood count (CBC) was analyzed from blood samples. Skin Prick Tests (SPTs) were performed on the forearm to common food allergens and aeroallergens in childhood atopic dermatitis (Dermatophagoides Pteronyssinus, Dermatophagoides farine, wheat, soya, cow's milk, egg and Peanut). All testes were done with histamine chloride 10 mg/ml as positive and sodium chloride 0.9% as negative controls. The histamine response was read after 10 minutes, and allergens and negative control after 15 minutes). SPTs were performed at first visit or at 5 months of age with commercial solutions (Stallergenes, Antony, France). A wheal diameter of 3 mm greater than the negative control was considered positive.

Statistical Analysis

Baseline characteristic of two groups were compared using the t-test and chi-square test. The primary outcome variable was the SCORAD index. Baseline SCORAD and after treatment SCORAD were compared by paired t test. Regression analysis was used to compare the SCORAD changes in the treatment groups with respect to different baseline potential predictive factors like age, sex, mode of delivery, personal and family history of atopy, number of siblings, previous history of hospitalization and antibiotic consumption, day care attendance, primary SCORAD, positive SPT, total IgE and eosinophil count at the start of the intervention. All statistical analyses were performed using SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA). A *p*-value of less than 0.05 was considered statistically significant for all analyses.

RESULTS

Among 48 infants who were referred to us with atopic dermatitis, seven children withdrew before beginning the intervention for personal reasons or severity of their disease [SCORAD index was less than 25(mild type)]. Forty-one patients were initially included after informed consent by their parents. There were 20 patients allocated to the synbiotic group and 21 patients to the placebo group. Five (three in placebo group and two in synbiotic group) did not complete the study. The reasons for exclusion during treatment were nonattendance to scheduled visits (synbiotic group, n: 1; placebo group, n: 2) and complain of diarrhea in a twin (synbiotic group, n: 1; placebo group n: 1). Finally 36 patients completed the trial.

The demographic and clinical characteristics of the study population are summarized in table 1. There was not any significant statistical difference in demographic, immunological blood parameters and

disease severity at baseline by comparing Synbiotic and Placebo groups.

Total and objective SCORAD index were measured at the baseline and after two months intervention with synbiotic or placebo. At entrance to study the mean total SCORAD was 40.93(synbiotic group 39.92 vs. placebo group 41.95) and the mean baseline objective SCORAD was 31.29 (synbiotic group 30.53 vs. placebo group 32.06). After two months of intervention, improvement in atopic dermatitis severity (Decreases in SCORAD index) was seen in two treatment groups (Decreases range in total SCORAD 4.00 to 58.50) but there was no statistical difference between synbiotic and placebo groups in the decrease of total and objective SCORAD.

The mean decrease of Total SCORAD was 23.26(placebo group 22.30 vs. synbiotic group 24.23) (Figure 1). The mean decrease of objective SCORAD was 16.63(placebo group 15.16 vs. synbiotic group 18.10) (Figure 2).

Table 1. Baseline demographic and clinical characteristics of study groups

Characteristics * †	Placebo	Synbiotic
Number of patients(N)	18	18
Gender, M/F N (%)	12/6 (%77,%33)	12/6 (%77,%33)
Mean age at study entry, months (SD)	14.7(6)	15.4(8.4)
Personal history of atopy N (%)	8 (%44)	5 (%27)
Family history of atopy N (%)	14 (%77)	15 (%83)
Have any Sibling N (%)	11 (%61)	10 (%15)
Total SCORAD index at inclusion, mean (SD)	39.9(11.6)	41.9(15.4)
Objective SCORAD index at inclusion, mean (SD)	30.5(9.8)	32.0(11.4)
Eosinophil count Cell/ μ L , Mean(SD)	312.9(201)	447.7(728)
IgE Iu/ml ,Mean(SD)	139.3(214.6)	71.6(149.9)
Sensitization (positive SPT to any allergens) (N (%))	6 (%33)	6 (%33)
Exclusive breast feed N (%)	13 (%72)	13 (%72)
Mean age at onset of AD, months(SD)	2.9 (1.2)	2.5 (1.2)
Type of delivery: C/S N (%)	13 (%72)	15 (%83)
History of antibiotic consumption N (%)	14 (%77)	13 (%72)
History of hospitalization N (%)	7 (%38)	6 (%33)
Mean family size N (SD)	3.7 (0.5)	4.2 (1.7)
Having any pet at home N (%)	0 (%0)	1 (%5)
History of day care attendance N (%)	2 (%11)	1(%5)
Having previous treatment N (%)	9 (%50)	13 (%72)
Low birth weight N (%)	1 (%5)	2 (%11)

N: number ,SD: Standard Deviation , %:Percent

* P-value < 0.05 was considered as significant difference which was determined by Pearson chi square for all nominal data.

† Not significant statistical difference was detected by comparing both groups

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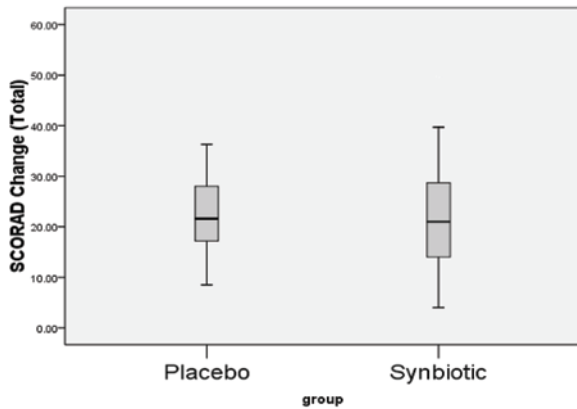


Figure 1. Change in Total SCORAD after treatment with placebo or Synbiotic

By additional statistical analysis we could not show difference between two treatment groups (synbiotic and placebo) in the decrease of total and objective SCORAD (result not shown). Additional analysis also was done regarding to primary subgroup conditions that may influence treatment response like age at entrance to the study, having sibling, type of delivery (NVD vs. C/S), history of atopy in patients and their families, antibiotic consumption, IgE and eosinophil levels in blood samples at entrance to study, and sensitization to tested any allergen (SPT $\geq$ 3mm).

Analysis of individual SCORAD components (extent, intensity and pruritus) by t test showed that patients in both groups with greater pruritus score had a greater decrease in objective SCORAD ($p=0.03$) and Total SCORAD ($p=0.01$) but this decrease was similar in synbiotic compared to placebo. Also patients who did not have any sibling showed a greater decrease in Total SCORAD ($p=0.03$) and Objective SCORAD ($p=0.01$) without difference between two groups.

DISCUSSION

In this randomized, double-blind, placebo-controlled study we evaluated the efficacy of synbiotic in treatment of atopic dermatitis. With regard to the fact that adding an appropriate prebiotic to probiotic can improve the viability and survival of probiotic strains.²⁶

Thus, we used synbiotic that could have better results in treatment than probiotics alone. Regarding to ethic commitment we gave similar low potent topical regimen (Hydrocortisone and Eucerin) to all patients (synbiotic and placebo groups).

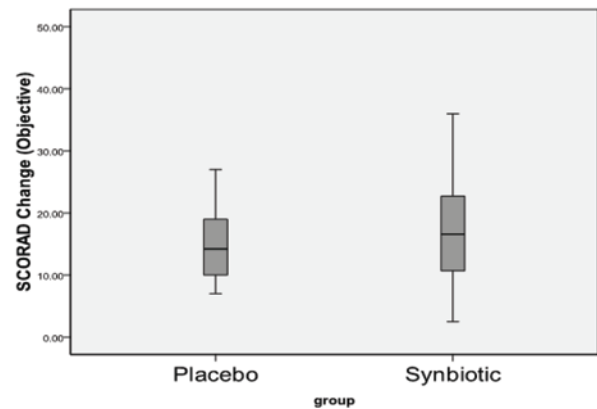


Figure 2. Change in Objective SCORAD after treatment with placebo or Synbiotic

We included only children with moderate to severe AD (mean SCORAD score of 40.93) in this study, since some previous studies showed more severe AD had a greater decrease in SCORAD in response to probiotic.²⁷ We also predicted that if children with mild disease enter to study they may completely resolve and we could not evaluate effect of synbiotic comparing to placebo. Although antibiotics and specific diets could have negative effect in our study and probably interfere with the colonization of probiotics, we did not restrict patient's diet or antibiotic, prior or during study, because this restriction could have had nutritional problem and severe infectious complications. After intervention both groups of patients (synbiotic and placebo groups) had a significant improvement in their AD severity (by decrease in SCORAD index). However, we could not show significant difference in SCORAD index decrease by administration of synbiotic as compared placebo in children with AD, and synbiotics appeared not superior to the placebo in treatment of atopic dermatitis.

We also performed subgroup analysis but we could not demonstrate significant benefit of synbiotic by subgroup analysis. For example in the patients with AD who concomitantly had or did not have Allergen sensitization (evaluated by SPT), decrease of AD severity was similar in both synbiotic and placebo groups. Although analysis showed that as a whole patients with greater pruritus score at entrance to study and patients who did not have any sibling at home had a greater decrease in Objective and Total SCORAD. This greater decrease was not seen if compared synbiotic with placebo group and decreases were identical in two groups.

The effect of probiotics in infants with atopic dermatitis first was evaluated by Majamaa and Isolauri in 1997. They showed that effect of probiotics was short time and, did not persist after probiotics had been discontinued.²⁸ Kirjavainen et al in another study suggested that probiotics were effective in early onset of atopic dermatitis.²⁹ In a randomized trial by Passeron et al, they suggested that synbiotics and prebiotics improve atopic dermatitis significantly in children over two years old.³⁰ Viljanen et al in the largest study to date evaluated the effect of probiotic in treatment of atopic dermatitis (n = 230). They did not find any difference between two intervention groups after four weeks of treatment and four weeks after treatment was discontinued.²² In a survey by Rosenfeldt et al. by using lyophilized probiotics in older children (average age 5.2 years), a significant decrease in SCORAD was seen only in a subgroup of children with elevated IgE levels and positive skin prick test.³¹ In another study by Sisteck et al probiotics were effective only in food-sensitized subset of children.²³ Brouwer and Folster Holst et al in two separate studies showed that probiotics were not effective in infants with atopic dermatitis.^{32,33} In a recent clinical trial by R Farid et al, they used a synbiotic similar to our study and showed a significant benefit of synbiotic in SCORAD index decrease compared to placebo.³⁴ The Possible explanations for different results of this study with other trials could be differences in the bacterial strains in different probiotics products, dose and duration which were used, host factors that could influence microbial colonization (like to hygiene level), allergic propensity, and other environmental factors that could influence immune system development and colonization of probiotic bacteria in the gut.

The results of this study are not in agreement with Kirjavainen, Passeron, Viljanen, Rosenfeldt and Sisteck who showed effectiveness of probiotic or synbiotic in patients with AD or in a subset of them. The difference between their results and ours could be due to the fact that an effective topical treatment in our study might have prevented us to recognize the effects of synbiotic. It could also be related to unrestricted diet which may have contained prebiotic or probiotic (like cereal and yoghurt), that could have affected on the treatment groups. Also treatment or follow-up duration might not be long enough to evaluate effect of synbiotic compared to placebo in treatment of atopic dermatitis. Small sample size might have affected our results and

probably with greater samples we could achieve significant results. Another reason that might have affected this study results is the gap between the beginning of AD manifestations (mean age: 2.7 months) and intervention with synbiotic (mean age: 15.1 months). However the significant decrease in both synbiotic and placebo groups SCORAD indexes (more than 50% decreases in Total and Objective SCORAD) were not justifiable to us. Although it may be due to natural course of atopic dermatitis or topical low potent regimen in both groups, but this is more rapid and more effective than usual course of disease and potency of our treatment. Our results were in agreement with Brouwer and Folster Holst which could not show efficacy of probiotic in atopic dermatitis regardless of allergen sensitization.

In conclusion, our results could not confirm synbiotic as an effective treatment for childhood AD. However, Probiotics and synbiotics may have a potential role in the treatment of atopic dermatitis, but studies to date have not been persuasive. There may be special subset which would be responsive to probiotic or synbiotic but further studies are needed to determine these suitable subgroups.

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