

Effect of *Lactobacillus sakei* supplementation in children with atopic eczema–dermatitis syndrome

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Background: Probiotics have been suggested to be useful in children with atopic eczema–dermatitis syndrome (AEDS).

Objective: To assess the clinical effect of *Lactobacillus sakei* supplementation in children with AEDS.

Methods: In a double-blind, placebo-controlled trial, children aged 2 to 10 years with AEDS with a minimum SCORing of Atopic Dermatitis (SCORAD) score of 25 were randomized to receive either daily *L sakei* KCTC 10755BP or daily placebo supplementation for 12 weeks. Changes in SCORAD scores and serum chemokine levels from baseline were evaluated.

Results: Eighty-eight children were enrolled, and 45 were allocated to probiotic treatment. Seventy-five children completed the study, with 4 dropouts in the probiotic group and 9 in the placebo group. At week 12, SCORAD total scores adjusted by pretreatment values were lower after probiotic treatment than after placebo treatment ($P = .01$). There was a 31% (13.1-point) improvement in mean disease activity with probiotic use compared with a 13% (5.2-point) improvement with placebo use ($P = .008$). Significant differences in favor of probiotic treatment were also observed in proportions of patients achieving improvement of at least 30% and 50%. Compared with placebo, probiotic administration was associated with lower pretreatment-adjusted serum levels of CCL17 and CCL27 ($P = .03$ for both), which were significantly correlated with SCORAD total score ($r = 0.59$ and 0.63 , respectively; $P < .001$).

Conclusions: Supplementation of *L sakei* in children with AEDS was associated with a substantial clinical improvement and a significant decrease in chemokine levels, reflecting the severity of AEDS.

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INTRODUCTION

Atopic eczema–dermatitis syndrome (AEDS) is a common chronic inflammatory skin disease that can be complicated by recurrent skin infections.¹ The increase in prevalence and the clinical challenge of management have highlighted the need to develop new therapeutic approaches to control AEDS. Based on the knowledge of potential benefits from modification of the gastrointestinal flora, obvious interests in the preventive and therapeutic role of probiotics in AEDS have been aroused. In particular, results of population-based studies^{2,3} suggest that childhood enteric infection and increased exposure to bacteria are protective against allergies, facilitating the clinical trial of probiotics for the management of AEDS.

Because rapid colonization occurs in the first year of life until a stable gut microflora is established,⁴ most previous

studies examined the effect of early probiotic supplementation. Perinatal administration of probiotics to at-risk infants halved the subsequent occurrence of AEDS in IgE-independent mechanisms.^{5,6} Probiotics were also shown to reduce the severity of AEDS when administered to infants with early-onset AEDS,^{7–9} although other clinical trials^{10,11} have not shown AEDS-related benefits of probiotic supplementation during infancy. In contrast, only a few clinical trials have evaluated the effectiveness of probiotics on older children with established AEDS. In these trials,^{12–14} the administration of probiotics to children 1 year and older seems able to improve the manifestations of AEDS.

The purpose of this study was to evaluate the clinical efficacy in AEDS of a newly identified probiotic strain, *Lactobacillus sakei* KCTC 10755BP, which showed the most potent inhibitory activity against *Staphylococcus aureus* growth among *Lactobacillus* species in a preliminary experiment. We administered *L sakei* to an unselected group of children aged 2 to 10 years with moderate and severe AEDS and evaluated the clinical outcome at the end of the intervention. In addition, we also measured levels of serum chemokines as activity markers for AEDS to provide more objective evidence for the beneficial role of this probiotic.

METHODS

Patients and Study Design

Children aged 2 to 10 years were recruited between January 1, 2007, and August 31, 2008, to study the effects of the

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probiotic on AEDS symptoms at the Department of Pediatrics, Chungbuk National University Hospital. AEDS was defined as a pruritic chronic or chronically relapsing noninfectious dermatitis with typical features and distribution as suggested by Hanifin.¹⁵ The inclusion criteria were AEDS present for at least 6 months, a SCORing of Atopic Dermatitis (SCORAD) total score greater than 25, and a change in the SCORAD total score of not more than 10% within 2 weeks. We excluded patients who had been treated with cyclosporine, systemic corticosteroids, topical calcineurin inhibitors, or Chinese herbal medicine during the preceding 3 months. Patients were randomized in a double-blind design to receive either probiotic or placebo treatment.

The bacterial preparation contained microcrystalline cellulose (1.76 g) as a carrier and freeze-dried *L sakei* KCTC 10755BP, which was shown to inhibit *S aureus* growth most potently among *Lactobacillus* species (data not shown). The count of viable cells contained in the freeze-dried bacterial preparations remained stable after 6 months of storage at 4°C. Each dose was stored in airtight alu-bags at 4°C until the last day of the intervention period. A dose of 5×10^9 colony-forming units of *L sakei* or an identical-appearing placebo preparation was given twice daily. The placebo preparation consisted of microcrystalline cellulose, same as the probiotic preparation. When administered to patients, the probiotic (or placebo) preparation was dissolved in 2.5 to 5.0 mL of water or any liquid preferred by the patient. Issues regarding the taste of the preparation and the child's preferred way to ingest the powder were discussed at each scheduled visit. None of the patients changed their diet during the study period.

During the study period, all of the patients were asked to take a bath once daily with warm water for 5 to 10 minutes and to apply an emollient immediately after bathing. Patients were permitted to use topical corticosteroids as required, and only 0.1% prednicarbate was prescribed to facilitate monitoring. A quantitative estimate of the use of prednicarbate, 0.1%, was made at each visit by weighing the medication tube. At enrollment, the levels of total serum IgE, eosinophil cationic protein, and specific IgE to common allergens in the Cheongju area, including *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, cat, dog, mugwort, *Alternaria alternata*, egg, milk, soy, and wheat, were determined by using CAP FEIA (Phadia Inc, Uppsala, Sweden). The study protocol included written consent by the parents of the participating patients and was approved by the institutional review board of Chungbuk National University.

Clinical Evaluation

The clinical severity of the eczema was evaluated at -2, 0 (baseline), 6, and 12 weeks. Each patient was examined by the same pediatrician at each visit. A standardized scoring system (SCORAD) developed by the European Task Force for Atopic Dermatitis was applied. This severity grading takes into account the intensity and extent of the eczema and subjective itch and sleep loss. The objective SCORAD score

(intensity and extent of the eczema) ranges from 0 to 83. When the subjective SCORAD score (pruritus and sleep loss) is added, the SCORAD total score can extend to a maximum of 103. As proposed by the European Task Force for Atopic Dermatitis, the eczema was graded as mild (SCORAD score, <25), moderate (SCORAD score, 25–50), or severe (SCORAD score, >50). At the final visit, the patients' or parents' opinions on the efficacy of the treatment and tolerance were recorded.

Chemokines in Serum

The serum levels of thymus and activation-regulated chemokine CCL17 and cutaneous T-cell-attracting chemokine CCL27 were measured by using a commercially available enzyme-linked immunosorbent assay kit (R&D Systems, Minneapolis, Minnesota). Briefly, 96-well polystyrene plates were coated overnight with purified mouse IgG anti-human CCL17 or CCL27 antibody. After washing, the plates were blocked for 1 hour with phosphate-buffered saline containing 1% bovine serum albumin. Standards and serum samples were added, and the plates were incubated for 2 hours. For CCL27 measurement, serum samples were added after making a 1:5 dilution with phosphate-buffered saline. After washing, the plates were incubated with biotinylated goat anti-human CCL17 or CCL27 antibody for 2 hours and then with streptavidin conjugated to horseradish peroxidase for 1 hour. Samples were developed with tetramethylbenzidine substrate diluted in a citrate phosphate buffer. Reactions were stopped by adding sulfuric acid, and the plates were read at 450 nm. The concentrations were calculated from a standard curve. Limits of detection for CCL17 and CCL27 were 7 and 16 pg/mL, respectively, whereas maximum levels of detection were 2000 and 4000 pg/mL, respectively.

IgE and Eosinophil Cationic Protein in Serum

Total and specific IgE levels were measured by using CAP FEIA. The cutoff value for a positive specific IgE antibody result was 0.35 IU/mL. Serum eosinophil cationic protein levels were determined by using the Pharmacia CAP system fluoroenzyme immunoassay, according to the manufacturer's standard procedures.

Statistical Analysis

We based sample size estimation on an estimate of a 30% response rate to treatment because a 30% reduction of symptoms in AEDS has been considered clinically relevant in previous clinical trials of probiotics.^{11,16} On this assumption, calculations indicated that 32 patients in each study arm were needed (80% power, 5% significance). We aimed to recruit 76 patients to allow for a 15% dropout rate. For demographic characteristics, the *t* test was used for continuous variables and the χ^2 test for categorical data. Analysis of covariance was used for multiple comparisons in which treatment groups were compared with each other regarding posttreatment values. Because differences existed in baseline SCORAD scores

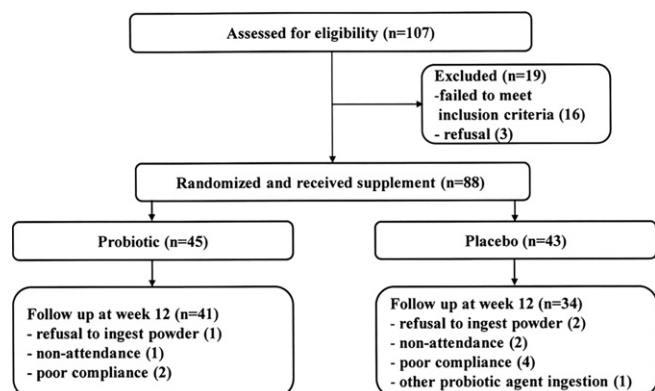


Figure 1. Trial profile showing patient populations analyzed for efficacy of the probiotic.

and chemokine levels (pretreatment values), these were taken as covariates in the analysis. The effect of the treatment was also calculated by comparing changes observed during active treatment with changes observed during placebo treatment (paired *t* test). The χ^2 test was used to estimate differences in proportions of patients achieving at least 30% and 50% reductions in the SCORAD score. Correlation coefficients between SCORAD scores and serum chemokine levels were determined by using the Spearman rank correlation test. The serum chemokine measurements were analyzed on the logarithmic scale. The amount of topical corticosteroid used during 12 weeks and change from baseline to week 12 in topical corticosteroid dose were compared using a Mann-Whitney test. A *P* < .05 was considered significant. Statistical analyses were performed using a commercially available software program (SPSS for Windows version 11.0; SPSS Inc, Chicago, Illinois).

RESULTS

Study Population

Of the 107 individuals who were screened, 88 met the entry criteria and were randomized to treatment, 45 to the probiotic group and 43 to the placebo group (Fig. 1). Of these patients, 13 were withdrawn because of refusal to ingest the powder, nonattendance at scheduled visits, poor compliance, and ingestion of other probiotic agents. No significant differences in dropout rates were observed between the groups (*P* = .11). Compliance was good, with 91% of doses administered and no difference between the 2 groups (*P* = .75). The full analysis set used for the efficacy analyses thus included 41 patients in the probiotic group and 34 patients in the placebo group. The characteristics of the study population are summarized in Table 1. No statistically significant differences were noted between the 2 groups based on sex, age, the presence of other atopic manifestations, sensitization status to inhalant and food allergens, levels of total IgE and eosinophil cationic protein, and SCORAD scores.

Clinical Effects

The mean SCORAD total score was significantly decreased in the probiotic (*P* < .001) and placebo (*P* = .007) groups from baseline. However, although there was no difference at week 6, pretreatment-adjusted SCORAD total scores at week 12 were significantly lower in the probiotic group than in the placebo group (*P* = .01) (Table 2). The mean change in SCORAD total score was −13.1 points (95% confidence interval, −17.5 to −8.6 points) in the probiotic group, which was significantly greater than the mean change of −5.2 points (95% confidence interval, −8.8 to −1.5 points) in the placebo group (*P* = .008). In addition, when the efficacy of probiotic supplementation in AEDS was assessed by comparing the proportion of patients who achieved at least 30% and

Table 1. Demographic Clinical Characteristics of the 75 Patients Enrolled in the Study

	Probiotic group (n = 41)	Placebo group (n = 34)	<i>P</i> value
Sex, M/F, No.	20/21	13/21	.36
Age, mean (range), y	6.3 (2.3–9.8)	5.8 (2.0–9.7)	.50
Age group, No. (%)			
2–6 y	25 (61)	22 (65)	.74
7–10 y	16 (39)	12 (35)	.74
Asthma or allergic rhinitis, No. (%)	22 (54)	18 (53)	.95
Sensitization, No. (%)			
Overall	34 (83)	28 (82)	.95
Aeroallergen	27 (66)	24 (71)	.66
Food allergen	22 (54)	19 (59)	.85
Log total IgE, mean (range), IU/mL	2.37 (0.96–3.38)	2.31 (1.18–3.66)	.69
Log ECP, mean (range), mg/dL	1.37 (0.30–2.23)	1.30 (0.43–2.29)	.51
SCORAD score, mean (range)			
Total	42.6 (26.4–75.7)	40.0 (27.2–76.5)	.50
Extent and intensity	32.4 (17.0–55.8)	31.0 (17.7–56.5)	.66
Pruritis and sleep loss	10.2 (1.0–20.0)	9.0 (3.0–20.0)	.29

Abbreviations: CI, confidence interval; ECP, eosinophil cationic protein; SCORAD, SCORing of Atopic Dermatitis.

Table 2. Pretreatment-Adjusted SCORAD Scores After Treatment With a Probiotic or Placebo^a

	Probiotic group (n = 41)	Placebo group (n = 34)	P value ^b
Week 6			
Total score	35.1 (32.2–38.0)	37.9 (34.7–41.1)	.19
Extent and intensity	26.8 (24.2–29.4)	30.5 (27.6–33.3)	.07
Itch and sleep loss	8.4 (7.5–9.3)	7.3 (6.4–8.3)	.12
Week 12			
Total score	28.8 (25.1–32.4)	35.8 (31.9–39.8)	.01
Extent and intensity	22.7 (19.8–25.6)	27.8 (24.7–31.0)	.02
Itch and sleep loss	6.1 (4.9–7.4)	7.9 (6.5–9.3)	.07

Abbreviation: SCORAD, SCORing of Atopic Dermatitis.

^a Values are presented as mean (95% confidence interval).

^b By analysis of covariance.

50% reductions in the SCORAD score, there was a significant difference between the probiotic and placebo groups (Fig. 2).

We also analyzed objective (intensity and extent of the eczema) and subjective (itch and sleep loss) SCORAD scores separately because extent of eczema was reported to correlate well with intensity but weakly with itch and sleep loss.¹⁷ After adjusting for baseline differences, mean objective and subjective scores at week 6 were not lower in the probiotic group compared with those in the placebo group. However, pretreatment-adjusted objective scores at week 12 were significantly lower in the probiotic group than in the placebo group ($P = .02$) (Table 2). Although pretreatment-adjusted subjective scores after 12-week probiotic treatment were lower compared with those after placebo treatment, the difference did not reach the level of significance.

Serum Levels of Chemokines

To provide laboratory evidence of the efficacy of the probiotic, we determined serum CCL17 and CCL27 levels, which were previously shown to correlate with the severity of AEDS.^{18,19} We also found a strong correlation between SCORAD total score and the serum levels of CCL17 and

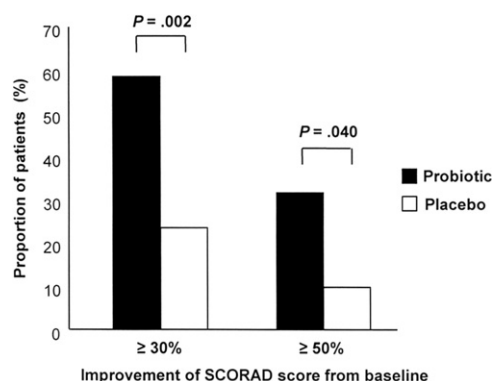


Figure 2. Patients achieving at least 30% and 50% improvement in SCORing of Atopic Dermatitis (SCORAD) scores at the study end point.

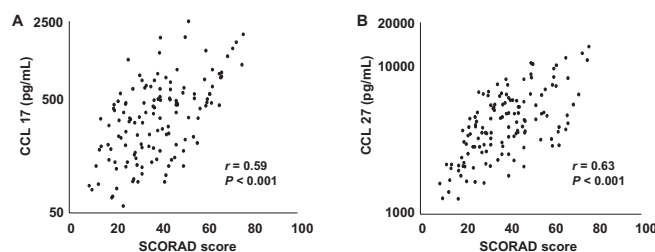


Figure 3. Correlation of serum logarithmic CCL17 (A) and CCL27 (B) levels with disease severity assessed by SCORing of Atopic Dermatitis (SCORAD) scores in 75 patients with atopic eczema–dermatitis syndrome.

CCL27 ($r = 0.59$ and 0.63 , respectively; $P < .001$) (Fig. 3). In addition, the changes during 12 weeks in serum CCL17 and CCL27 levels correlated with the changes during the same period in SCORAD total scores ($r = 0.40$ and 0.44 , respectively; $P < .001$). In patients treated with the probiotic, serum CCL17 and CCL27 levels were significantly decreased from baseline at the end of the intervention ($P < .001$ for both). In contrast, decreases in serum CCL17 ($P = .20$) and CCL27 ($P = .70$) levels in the placebo group did not reach the level of significance. After 12 weeks, pretreatment-adjusted serum CCL17 and CCL27 levels were significantly lower in the probiotic group than in the placebo group ($P = .03$ for both) (Table 3).

Use of Topical Corticosteroids

In the probiotic group, 22 of 41 patients (54%) used topical corticosteroids during the intervention compared with 20 of 34 (59%) in the placebo group. The median total use of prednicarbate throughout the trial in the probiotic vs placebo group was 11 g (range, 0–63 g) vs 13 g (range, 0–83 g) ($P = .62$). The median change from baseline at week 12 in the amount of topical corticosteroids used for 1 week was -0.5 g (range, -2.7 to 1.3 g) in the probiotic group and -0.3 g (range, -1.9 to 2.5 g) in the placebo group ($P = .64$).

Table 3. Serum Pretreatment and Posttreatment Values of TARC/CCL17 and CTACK/CCL27 in the Probiotic and Placebo Groups^a

	Probiotic group (n = 41)	Placebo group (n = 34)	P value
Log TARC/CCL17, pg/mL			
Baseline	2.60 (2.50–2.70)	2.50 (2.35–2.64)	.24
Week 12 ^b	2.27 (2.14–2.40)	2.48 (2.33–2.62)	.03
Log CTACK/CCL27, pg/mL			
Baseline	3.68 (3.60–3.76)	3.63 (3.53–3.73)	.46
Week 12 ^b	3.52 (3.45–3.59)	3.62 (3.54–3.70)	.03

Abbreviations: CTACK, cutaneous T-cell-attracting chemokines; TARC, thymus and activation-regulated chemokines.

^a Values are presented as mean (95% confidence interval).

^b Adjusted by the pretreatment value.

DISCUSSION

Current evidence is more convincing for the efficacy of probiotics in the prevention rather than the treatment of AEDS.²⁰ However, despite the mixed results in clinical trials^{7–11} evaluating the therapeutic potential of probiotics during infancy or childhood including infancy, data in clinical trials^{12–14} for the treatment of established AEDS seem to be favorable in children older than 1 year. We also examined the beneficial role of probiotics in older children aged 2 to 10 years with chronic moderate-to-severe AEDS by administering *L sakei*. In our preliminary experiment, *L sakei* among *Lactobacillus* species showed the most potent inhibitory activity against the growth of *S aureus*, which has been suggested to contribute to the exacerbation of AEDS.^{21–23} This finding raises a possibility that the beneficial role of *L sakei* in AEDS might be related to the inhibitory effect of this probiotic on *S aureus*. However, further investigations are required to provide evidence of the relationship between probiotic-induced suppression of *S aureus* growth and clinical improvement. Another possible mechanism underlying the role of *L sakei* in AEDS was suggested in a previous study²⁴ showing that *L sakei* was effective in reducing allergen-induced skin inflammation through the regulation of elevated IgE and interleukin 4 levels in allergen-sensitized mice. Together with evidence that probiotics are vital to the healthy maturation of the immune system after birth,²⁵ this study implies an immunomodulatory role of *L sakei* in AEDS.

At the end of treatment, pretreatment-adjusted SCORAD total scores were significantly lower in the probiotic group than in the placebo group. In addition, the SCORAD change of –13.1 points (31% improvement from baseline) in the probiotic group was significantly greater than the –5.2 points (13% improvement from baseline) in the placebo group. A SCORAD reduction in the probiotic group was greater than 30% improvement, which was considered clinically meaningful in previous trials for AEDS,^{11,16} and also greater than the normal variation of stable AEDS, which was previously defined as less than or equal to 11 points on the SCORAD scale.¹⁴ Therefore, administration of *L sakei* to children with AEDS seems to be associated with an improvement in the clinical severity of eczema. In addition, by comparing the proportion of patients achieving at least 30% and 50% reductions in the SCORAD score between the probiotic and placebo groups, we provided further evidence for better clinical outcomes in patients receiving the probiotic.

Daily bathing with immediate application of emollient recommended to all participants might induce a significant decrease in SCORAD scores in both groups. The improving effect of bathing with emollient application on itch and sleep loss might also be a reason why there was no statistically significant difference in pretreatment-adjusted subjective scores after 12-week treatment between groups. In addition, the improvement in AEDS detected in both groups might come from the therapeutic effect of topical corticosteroids

because enrolled patients were allowed to use topical corticosteroids as needed. However, the greater improvement detected in the probiotic group does not seem to be linked to the use of topical corticosteroids because the amount of topical corticosteroid used during the intervention was similar between the 2 groups.

We also monitored changes in CCL17 and CCL27 levels to provide laboratory evidence of the efficacy of the probiotic. CCL17 and CCL27 are thought to play an important role in tissue-specific homing of T cells to skin^{26,27} and have been suggested as useful objective and specific markers for disease severity in AEDS.^{18,19} We show herein that CCL17 and CCL27 serum levels correlate well with the severity of AEDS. This correlation substantiates the usefulness of CCL17 and CCL27 as objective markers for the disease severity of AEDS in evaluating the efficacy of treatment with the probiotic. Therefore, significant reduction of these chemokines in patients receiving the probiotic strengthens the evidence base for a beneficial role of probiotic administration to children with AEDS. In addition, because interferon gamma was previously reported to contribute to chronic skin inflammation in AEDS through the induction of CCL17,²⁸ lower levels of CCL17 in patients receiving the probiotic raise the possibility of a dampened interferon gamma response in these patients.

One limitation in this study is the lack of a variable that accounts for the allergic constitution of the host, which has been observed to affect the response to probiotics.^{9,13} However, the confounding potential of the sensitization status of individual patients seems to be low in this study because there was no significant difference in allergic constitution between the 2 groups. Another limitation that we have considered is the possibility of failure to capture the fluctuating nature of the AEDS. Disease activity in AEDS can fluctuate widely in the short-term,²⁹ and, consequently, isolated measurements might be unable to indicate the underlying trend and lead to incorrect conclusions. Therefore, although the SCORAD score decrease was of greater magnitude in the probiotic group than in the placebo group during 12 weeks of treatment, more prolonged observation to assess the efficacy of probiotics seems to be required.

In summary, this study provides evidence that administration of the probiotic strain *L sakei* may be associated with improvement in the clinical severity of AEDS and a decrease in chemokine levels, reflecting the severity of disease in patients with established AEDS. The effect of probiotic supplementation seemed to be selective because levels of responsiveness were different between patients receiving the probiotic. A prolonged period of observation is needed to provide more convincing evidence of the efficacy of *L sakei* in AEDS.

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