Brief communication

Probiotics during pregnancy and breast-feeding might confer immunomodulatory protection against atopic disease in the infant

Samuli Rautava, MD, Marko Kalliomäki, MD, and Erika Isolauri, MD, PhD
Turku, Finland

The prevalence of atopic diseases is increasing throughout the Western world, and means of primary prevention are needed to reverse this trend. The role of breast-feeding, the best source of infant nutrition, in protection against atopic disease remains elusive. In this double-blinded, placebo-controlled study of 62 mother-infant pairs, it is shown that administering probiotics to the pregnant and lactating mother increased the immunoprotective potential of breast milk, as assessed by the amount of anti-inflammatory transforming growth factor β2 (TGF-β2) in the milk (2885 pg/mL [95% CI, 1624-4146] in mothers receiving probiotics vs 1340 pg/mL [95% CI, 978-1702] in mothers receiving placebo; *P* = .018). The risk of developing atopic eczema during the first 2 years of life in infants whose mothers received probiotics was significantly reduced in comparison with that in infants whose mothers received placebo (15% and 47%, respectively; relative risk, 0.32 [95% CI, 0.12-0.85]; *P* = .0098). Maternal atopy was a clear risk factor for atopic eczema in the infant. The infants most likely to benefit from maternal probiotic supplementation were those with an elevated cord blood IgE concentration. Administering probiotics during pregnancy and breast-feeding thus offers a safe and effective mode of promoting the immunoprotective potential of breast-feeding and provides protection against atopic eczema during the first 2 years of life. (J Allergy Clin Immunol 2002;109:119-21.)

Key words: *Atopic dermatitis, breast-feeding, infant, primary prevention, probiotics*

There is a strong hereditary component in the development of atopic diseases, and maternal atopic disease in particular constitutes a risk for the infant.[1] However, genetic factors are unlikely to explain recent increases in the prevalence of atopic diseases in developed countries. Novel approaches to prevention are urgently needed to reverse this trend. Of the preventive measures previously investigated, only breast-feeding is still recommended as potentially beneficial.

Abbreviation used
TGF-β: Transforming growth factor β

In addition to optimal nutrients for growth and development, breast-feeding provides immunologic protection during a critical period of life when the infant´s own immune defence mechanisms are immature. Transforming growth factor β (TGF-β) is considered a key immunoregulatory factor in promoting IgA production and induction of oral tolerance.[2,3] During the early postnatal period, when endogenous TGF-β production in the intestine is sparse, maternal milk constitutes an important exogenous source. A recent study has shown that the TGF-β concentration in maternal colostrum correlates with both the infant's ability to produce specific IgA antibodies against dietary antigens and prevention of atopic disease during exclusive breast-feeding.[4] Accordingly, the conflicting data on the preventive potential of breastmilk might be explained by differences in breast milk composition.

Probiotics, live microbial food ingredients beneficial to health, have been shown to control allergic inflammation and alleviate symptoms associated with atopic eczema and food allergy, partly by the merit of enhanced production of TGF-β.[5] We therefore investigated whether the immunoprotective potential of breast-feeding could be promoted by administering probiotics to the pregnant and lactating mother with and without atopic disease.

SUBJECTS AND METHODS

This study was conducted as a part of a double-blinded, placebo-controlled trial evaluating the preventive potential of probiotics in allergy, as described in detail elsewhere.[6] In all, 159 pregnant women from atopic families were randomized to receive either *Lactobacillus rhamnosus* strain GG (ATCC 53103; daily dose, 2×10^{10} colony forming units; Valio Ltd, Helsinki, Finland), or placebo (microcrystalline cellulose; Valio Ltd) during the 4 weeks before giving birth (mean, 28 days; 95% CI, 24-31) and during breast-feeding. Criteria for inclusion in this part of the study, which 62 mothers and infants fulfilled, were breast-feeding and the maternal use of probiotics or placebo until the child was 3 months of age.

The concentration of serum total IgE was measured from cord blood. Through use of ELISA, the concentrations of TGF-β1 and TGF-β2 were measured from breast milk samples collected when the

From the Department of Paediatrics, University of Turku.
Supported by the Academy of Finland.
Received for publication June 1, 2001; revised September 12, 2001; accepted for publication September 20, 2001.
Reprint requests: Samuli Rautava, MD, Department of Paediatrics, University of Turku, PO Box 52, FIN-20521, Turku, Finland.

0091-6749/2002 $35.00 + 0 **1/85/120273**
doi:10.1067/mai.2002.120273

TABLE I. Baseline characteristics, clinical history, and clinical outcome

	Probiotics (n = 30)	Placebo (n = 32)
Baseline characteristics and clinical history		
Gestational age: mean (95% CI)	39.5 wk (38.9-40.0)	39.4 wk* (38.9-40.0)
Birthweight: mean (95% CI)	3650 g (3450-3850)	3520 g* (3340-3700)
Caesarian section	4/30 (13%)	4/32 (13%)†
Maternal atopic disease	18/30 (60%)	24/32 (75%) †
Older siblings	11/30 (37%)	12/32 (38%)†
Elevated cord blood IgE (≥0.5 kU/L)	10/24 (42%)	9/28 (32%)†
Exclusive breast-feeding: mean (95% CI)	3.2 mo (2.6-3.7)	3.2 mo (2.6-3.8)*
Total breast-feeding: mean (95% CI)	8.3 mo (7.2-9.5)	8.5 mo (7.0-10.0)*
Clinical outcome at 24 mo‡		
Chronic relapsing atopic eczema	4/27 (15%)	14/30 (47%)§
Gastrointestinal symptoms‖	2/28 (7%)	2/31 (6%)†
Cow's milk allergy	6/29 (21%)	3/31 (10%)†
Positive skin prick test result	6/26 (23%)	6/29 (21%)†
Serum IgE: median (IQR)	29 kU/L (18-46)	28 kU/L (14-108)¶
Specific IgE antibodies (≥0.35 kU/L)	8/29 (28%)	11/30 (37%)†

*Student *t* test; not statistically significant.
†χ^2 test; not statistically significant.
‡Differences in the numbers of infants in the groups are due to missing data in the clinical follow-up.
§χ^2 test; $P = .0098$.
‖Gastrointestinal symptoms related to food allergy as documented in a double-blinded, placebo-controlled cow's milk challenge.
¶Mann-Whitney test; not statistically significant.

infant was 3 months old.[4] The infants' clinical history and status were assessed at scheduled visits at the ages of 3, 6, 12, 18, and 24 months. The assessment of maternal atopic disease was based on reported clinical history of atopic eczema, allergic rhinoconjunctivitis, or asthma.

Atopic eczema was confirmed if the following features were detected: pruritus, typical morphology and distribution, and a chronic relapsing course. A family history of atopy was an inclusion criterion for the study. The chronicity criterion for atopic eczema was fulfilled if the infant had 3 or more episodes of eczema (each with a duration of at least 1 month) during the first two years of life. Eczema was considered transient if there were 1 or 2 such episodes. Cow's milk allergy was confirmed by a double-blinded, placebo-controlled cow's milk challenge, as described elsewhere,[7] when symptoms, clinical signs, or skin prick test results were suggestive of cow's milk allergy.

Data are expressed as means with 95% CIs, and the Student *t* test was applied to compare values between 2 groups in case of normally distributed data. Data of skewed distribution are expressed as medians with interquartile ranges; comparisons between groups were made through use of the Mann-Whitney *U* test. The χ^2 test was used in comparisons of proportions between groups.

RESULTS

The infants born to mothers receiving probiotics and those born to mothers receiving placebo were comparable with respect to mode of delivery, maternal atopic disease, and whether there were older siblings in the family, as well as mean duration of exclusive and total breast-feeding (Table I).

The concentration of TGF-β2 in the breast milk of mothers receiving probiotics was higher (2885 pg/mL [95% CI, 1624-4146]) than that in the breast milk of mothers receiving placebo (1340 pg/mL [95% CI, 978-1702]; $P = .018$). The respective concentrations of TGF-β1 were 226 ng/mL (95% CI, 118-335) and 178 ng/mL (95% CI 122-233; $P = .41$). In a subgroup of infants (n = 19) in whom the umbilical cord blood IgE concentration was above the detection limit (≥0.5 kU/L), the concentration of TGF-β2 in the breast milk of probiotic-treated mothers was 5085 pg/mL (95% CI, 1818-8352 pg/mL); this compared with 1136 pg/mL (95% CI, 532-1740 pg/mL) in the case of mothers who received placebo ($P = .021$).

In the clinical follow-up, data were obtained from 57 (92%) of 62 children up to the age of 2 years (Table I). In all, 35 children (61%) manifested eczema during the first 2 years of life, 17 (30%) of 57 with transient and 18 (32%) of 57 with chronic relapsing atopic eczema; 22 (39%) children were healthy. The risk of chronic relapsing atopic eczema during the first 2 years of life was significantly higher in children whose mothers had atopic disease (16 [42%] of 38) than in those with healthy mothers (2 [11%] of 19; relative risk, 4.0; 95% CI, 1.0-15.6; $P = .016$). Maternal intake of probiotics was associated with reduction in the prevalence of atopic eczema in comparison with placebo: 4 (15%) of 27 infants of mothers receiving probiotics had chronic relapsing atopic eczema, in comparison with 14 (47%) of 30 infants of mothers on placebo (relative risk, 0.32 [95% CI, 0.12-0.85]; $P = .0098$). The same trend was seen in infants born to atopic mothers as well as infants born to nonatopic mothers: in all, 4 (25%) of 16 infants whose mothers with atopic disease received probiotics developed chronic relapsing eczema, in comparison with 12 (55%) of 22 infants born to those receiving placebo (relative risk, 0.46 [95% CI, 0.18-1.16]; $P = .069$), and none of the 11 infants born to nonatopic mothers receiving probiotics developed chronic relapsing atopic eczema. No adverse reactions or clinical side effects were observed during probiotic supplementation or clinical follow-up.

DISCUSSION

Probiotics were shown here to confer protection from atopic eczema for the infant when administered to the mother before delivery and during breast-feeding. Infants with an elevated cord blood IgE concentration, considered to reflect atopic sensitization in utero, were most likely to benefit from these agents, inasmuch as probiotics increased the amount of TGF-β2 in breast milk. This suggests that probiotics exert their effect on the early immunologic mechanisms involved in the development of atopy and atopic disease, and it emphasizes the complex interactions among genetic predisposition, early sensitization, and immunoprotective factors in the development of atopy.

Fetal immune responses are constitutively T_H2-skewed, and this type of immune responsiveness is considered pivotal in the development of atopy and atopic disease. During the early postnatal period, an age-dependent decline in T_H2 responses in nonatopic children and a converse pattern in atopic children has been suggested.[8] Nevertheless, elevated serum IgE antibody concentrations early in life fail to correlate reliably with the future atopic status of the infant, and the predictive value of cord blood IgE antibody concentration is thus considered poor.[1] In this study, the administration of probiotics, albeit protective against atopic eczema, had no effect on the traditional objective correlates of atopy and atopic disease (ie, skin prick test results and serum IgE antibodies), which supports this concept. No direct correlation was observed between breast milk TGF-β2 concentrations and the development of atopic disease or atopy, as assessed with skin prick tests and serum IgE antibodies.

To conclude: First, infants who develop atopic disease might have a defect in the suppressive mechanisms primed to assimilate potentially allergenic challenges, and probiotics might promote these immunomodulatory mechanisms. The infants who develop atopic disease despite probiotic supplementation might exhibit defective responses to the immunomodulation provided by probiotics or TGF-β.

Second, administration of probiotics to the mother during pregnancy and breast-feeding appears to be a safe and effective mode of enhancing the immunoprotective potential of breast milk and preventing atopic eczema in the infant. Infants most likely to benefit from probiotics might be those with an elevated cord blood IgE concentration.

REFERENCES

1. Bergmann RL, Edenharter G, Bergmann KE, Guggenmoos-Holzmann I, Forster J, Bauer CP, et al. Predictability of early atopy by cord blood-IgE and parental history. Clin Exp Allergy 1997;27:752-60.
2. Stavnezer J. Regulation of antibody production and class switching by TGF-beta. J Immunol 1995;155:1647-51.
3. Petiprez K, Khalife J, Cetre C, Fontaine J, Lafitte S, Capron A, et al. Cytokine mRNA expression in lymphoid organs associated with the expression of IgA response in the rat. Scand J Immunol 1999;49:14-20.
4. Kalliomäki M, Ouwehand A, Arvilommi H, Kero P, Isolauri E. Transforming gowth factor-β in breast milk: a potential regulator of atopic disease at an early age. J Allergy Clin Immunol 1999;104:1251-7.
5. Isolauri E, Arvola T, Sütas Y, Moilanen E, Salminen S. Probiotics in the management of atopic eczema. Clin Exp Allergy 2000;30:1604-10.
6. Kalliomäki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in the primary prevention of atopic disease: a randomised, placebo-controlled trial. Lancet 2001;357:1076-9.
7. Isolauri E, Sütas Y, Mäkinen-Kiljunen S, Oja SS, Isosomppi R, Turjanmaa K. Efficacy and safety of hydrolyzed cow milk and amino acid-derived formulas in infants with cow milk allergy. J Pediatr 1995;127:550-7.
8. Prescott SL, Macaubas C, Smallacombe T, Holt BJ, Sly PD, Holt PG. Development of allergen-specific T-cell memory in atopic and normal children. Lancet 1999;353:196-200.