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4. Probiotics, breastfeeding and atopic eczema

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This article focuses on several aspects as follows; the relationship between permeability of the gastrointestinal tract and atopic eczema, probiotics and eczema, probiotics and the immune system in the gastrointestinal tract, breastfeeding and immunomodulation, and the relation between breastfeeding and the development of atopic eczema. It is concluded that there is evidence that some probiotic strains seem to be beneficial in the treatment of atopic eczema.

GUT MUCOSAL BARRIER AND ATOPIC ECZEMA

The gut mucosal barrier of patients with atopic eczema is impaired. In an *in vitro* study Majamaa & Isolauri (1) studied the absorption of horseradish peroxidase (HRP) through the gut mucosal barrier. Small intestinal biopsies were studied in Ussing chambers, measuring the absorption of both intact and degraded HRP. Compared with controls, absorption in patients with atopic eczema is increased.

There are also several studies showing increased intestinal permeability in patients with bronchial asthma. Benard et al. (2) studied the urinary excretion of Cr EDTA, a recognized method of monitoring intestinal absorption, in asthmatics, in patients with chronic obstructive airways disease and in controls. There were significant differences between the asthmatics and the other two groups in respect of increased intestinal permeability. There was no significant difference in intestinal permeability between patients with allergic and non-allergic asthma, and the intestinal permeability was not correlated with the severity of asthma as measured by FEV1.

We have studied intestinal permeability in atopic eczema sufferers using the relative urinary excretion of lactulose and mannitol following oral administration, expressed as the lactulose:mannitol (LM) ratio (3). Lactulose is not normally absorbed, whilst mannitol is absorbed but reduced whenever there is damage to the intestinal mucosa. Intestinal permeability is increased in relation to the severity of the atopic eczema as defined by the SCORAD index (4).

PROBIOTICS AND ATOPIC ECZEMA

Probiotics are live microorganisms that when ingested have a positive effect on the prevention or treatment of specific pathologic conditions. Probiotics are often lactobacilli and bifidobacteria. There are several studies which have looked at the relationship between probiotics and atopic eczema. Kalliomaki et al. (5) looked at the neonatal gut flora as a predictor of the development of atopic eczema in infants from high-risk families. Seventy-six infants from high-risk families had their intestinal flora examined at the age of 3 weeks with fluorescence *in situ* hydridization (FISH). In the 24 infants who developed atopic eczema, the ratio between the numbers of clostridia and lactobacilli in the gut flora was significantly greater (clostridia 9.3×10^7, lactobacilli 1.8×10^7; ratio 5.2) than in the 54 children who were non-atopic (clostridia 3.3×10^7, lactobacilli 6.1×10^7; ratio 0.54). These data suggest that differences in the neonatal gut microflora precede the development of atopy.

The intestinal flora seems to be influenced by mode of delivery for up to at least 12 months after birth. There are also data suggesting that children delivered by ceasarean section are more likely to develop type I allergies. Among children whose mothers were allergic, caesarean section was associated with a sevenfold increased risk of reactions to egg, fish or nuts (odds ratio 7.0; 95% CI 1.8–28; $p=0.05$) and a fourfold increased risk of confirmed egg allergy (odds ratio 4.1; 95% CI 0.9–19; $p=0.08$) (6). These observations support the theory that factors interfering with the colonization process might play a role in the development of food allergy. The hypothesis is then that if a child is delivered by caesarean section, it is more likely to be colonized by 'hospital microflora' than the 'mother's flora'.

The effect of perinatally administered *Lactobacillus* GG (LGG group) on the development of atopic eczema has been studied in a double-blind placebo-controlled study (7). The interventions took place from 4 weeks prior to delivery (mother) to 6 months after delivery (mother and infant). Of 53 infants in the LGG group, 14 developed atopic eczema by the age of 4 years compared with 25 of 54 in the placebo group (odds ratio 0.57; 95% CI 0.33–0.97).

We have evaluated the clinical and anti-inflammatory effect of probiotic supplementation in children with atopic dermatitis (AD) (8). In a double-blind, placebo-controlled, crossover study, two probiotic *Lactobacillus* strains (lyophilized *Lactobacillus rhamnosus* 19070-2 and *Lactobacillus reuteri* DSM 122460 selected by screening over 50 different strains for relevant properties,

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including adherence to the intestinal flora), were given in combination for 6 weeks to 41 children aged 1–13 years with moderate and severe AD. After active treatment 56% of patients experienced improvement in eczema, whereas only 15% of patients given placebo felt that their eczema had improved ($p=0.001$) based on the patient global assessment. There was, however, no change in total SCORAD. The extent of eczema decreased during active treatment from 18.2% to 13.7% ($p=0.02$). SCORAD decreased significantly in allergic patients (one skin prick and elevated IgE) ($p=0.02$), and S-eosinophil cationic protein also decreased during active treatment ($p=0.03$). The LM ratio, a measure of intestinal permeability, was also monitored in this study. The LM ratio was directly related to the severity of AD, and the intervention with probiotics reduced the permeability significantly (3). The study concluded that the probiotic *Lactobacillus* strains were beneficial in the management of AD, particularly in patients with a positive skin prick test and increased IgE levels.

PROBIOTICS AND GASTROINTESTINAL IMMUNITY

Dendritic cells reside in the gut mucosa and capture antigen. They play an important immunoregulatory role and have a strong effect on the Th1, Th2 and Th3 balance. They are modulated by the intestinal flora including probiotics. In an *in vitro* study Christensen et al. (9) exposed bone marrow-derived murine dendritic cells to different *Latobacillus* species and measured cytokine production. There were substantial differences among strains in the capacity to produce IL-12 and TNF-alpha and less pronounced effects on the production of IL-6 and IL-10. These results suggest that different probiotics can have very different effects on the dendritic cells in the intestine and thereby on the immune system. These observations could explain the varying efficacy observed in studies involving probiotics. The role of some probiotics is well established in treatment of acute infectious diarrhoea, but it is still too early to conclude on the effect in allergic diseases.

BREASTFEEDING AND IMMUNO-MODULATION

Human breast milk contains a wide variety of immune factors. There are leucocytes including B lymphocytes, macrophages, neutrophils and T lymphocytes; secretory immunoglobulin A and oligosaccharides, Bifidus factor, lysozyme, lactoferrin, gamma interferon, nucleotides and cytokines. Breastfeeding offers passive protection against gastrointestinal and to some degree respiratory tract infection. There are data which suggest it may also affect the child's own immune system. The size of the neonatal thymus has been measured in children, in relation to mode of feeding. At the age of 4 months the size of the thymic gland was about half the size in formula-fed infants compared to breastfed infants (10). There are also studies which show that the immune response after some vaccines is better in breastfed infants, tuberculin reactivity is transmitted with breast milk, and kidney transplants from a maternal donor survive better if the recipient has been breastfed (11). In accordance with these effects on the immune system there are data which suggest a protective effect against some immune-related diseases later on in life; for example, type 1 diabetes, Crohn's disease, coeliac disease and malignant lymphoma (12).

BREASTFEEDING AND ATOPIC ECZEMA

The relationship between breastfeeding and onset of atopic eczema in published studies has been assessed in a meta-analysis of prospective studies (13). If there is a family history, there is a significant protective effect of breastfeeding. In studies of the general population this effect is lessened and in families with no family history it is negligible.

A review of the literature from 1966 to 2001 concluded that breastfeeding seemed to protect from the development of atopic disease and the effect was stronger in children with atopic heredity (14). The review also concluded that breastfeeding protects against the development of atopic eczema. Another study was published whilst the meta-analysis was in press (15). This study, which included 1314 infants followed for 7 years, came to a different result and concluded that there was an increased risk for each additional month of breastfeeding.

The results overall present a rather mixed picture. The effect of confounding aspects, including socio-economic status, cannot always be addressed. Similarly, there are inherent problems in investigating the effect of breastfeeding. It is not possible to randomize patients into breastfeeding and non-breastfeeding groups for obvious ethical reasons. However, this was managed in a large prospective study investigating the effects of breastfeeding in Belarus (16). A total of 31 maternity hospitals were randomized to breastfeeding promotion or none. The results show that infants from intervention hospitals were more likely to be exclusively breastfed at 3 months of age (43% vs 6%). Atopic eczema in the intervention group was 3.3% versus 6.3% in the non-intervention group (adjusted OR 0.54; 95% CI 0.31–0.95).

CONCLUSION

There is evidence that some probiotic strains seem to be beneficial in the treatment of atopic eczema. A plausible mechanism for their effect is through a reduction of the increased intestinal permeability observed in the

condition. The immunomodulatory potential of different probiotic strains differs considerably.

The effect of breastfeeding in prevention of atopic eczema is not clear. However, with a family history of allergic disease there seems to be a clear effect. There is a need for a better understanding of the immunomodulatory effects of intestinal flora, probiotics and breastfeeding to fully understand how these early factors can influence the risk of atopic eczema.

DISCUSSION

Taieb; Do you know what accounts for the difference in the IL-10 response in murine cells to the different lactic acid bacteria?

Michaelsen; The actual mechanism responsible for the difference is not known.

Thestrup-Pedersen; We have found a similar difference amongst strains in affecting monocytes *in vitro*.

Michaelsen; We have not been able to account for the differences and of course only a few of the bacteria are available commercially.

Taieb; There are major differences between murine and human cells so caution is needed in extrapolating the data to the humans.

Michaelsen; Yes, therefore our next step is to repeat these experiments using human cells. Clinical studies in paediatrics are of course difficult.

Leung; Are these strains stable *in vivo*?

Michaelsen; Yes, these strains are well characterized. Their use in infectious diarrhoea is well documented. However, not all of these preparations are available commercially in Denmark. Many are available in health stores. Probiotic strains in yoghurt are not efficient probiotics.

Leung; Does breastfeeding influence the incidence of eczema later in life? There is evidence that if the mother is highly atopic, there is no effect.

Michaelsen; Some studies show that mothers with allergic disease are more likely to transmit it to their offspring if breastfeeding, but others show the opposite.

Leung; Is the breast milk of atopic and non-atopic mothers different?

Michaelsen; There appear to be differences in fatty acid composition. Fatty acids can affect the immune response.

Leung; Since many atopic mothers have *S. aureus* on their eczema, does breastfeeding transmit *S. aureus* to the intestinal flora of the infant?

Michaelsen; That I do not know, but infants not breastfed have more lactobacilli, bifidobacteria and clostridia.

Thestrup-Pedersen; In Germany, are probiotics used?

Diepgen; Patients are asking about them all the time.

Leung; What about France?

Taieb; There are plans to do studies with probiotics. There is a lot of commercial interest in this area.

Leung; What about BCG? Is there an interest in Scandinavia?

Thestrup-Pedersen; Not that I am aware of. Overall, it is fair to sum up that the situation concerning the use of probiotics is very complex.

REFERENCES

1. Majamaa H, Isolauri E. Evaluation of the gut mucosal barrier: evidence for increased antigen transfer in children with atopic eczema. J Allergy Clin Immunol 1996; 97: 985–990.
2. Benard A, Desreumeaux P, Huglo D, Hoorelbeke A, Tonnel AB, Wallaert B. Increased intestinal permeability in bronchial asthma. J Allergy Clin Immunol 1996; 97: 1173–1178.
3. Rosenfeldt V, Benfelt E, Valerius NH, Paerregaard A, Michaelsen KF. Effect of probiotics on gastrointestinal symptoms and small intestinal permeability in children with atopic dermatitis. J Pediatr 2004; 145: 612–616.
4. Consensus report of the European Task Force on atopic dermatitis. Severity scoring of atopic dermatitis: the SCORAD Index. Dermatology 1993; 186: 23–31.
5. Kalliomaki M, Kirjavainen P, Eerola E, Kero P, Salminen S, Isolauri E. Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing. J Allergy Clin Immunol 2001; 107: 129–134.
6. Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by caesarean section a risk factor for food allergy? J Allergy Clin Immunol 2003; 112: 420–426.
7. Kalliomaki M, Saliminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up randomised placebo-controlled trial. Lancet 2003; 361: 1869–1871.
8. Rosenfeldt V, Benfeldt E, Nielsen SD, Michaelsen KF, Jeppesen DT, Valerius NH, et al. Effect of probiotic *Lactobacillus* strains in children with atopic dermatitis. J Allergy Clin Immunol 2003; 111: 389–395.
9. Christensen HR, Frokiaer H, Pestka JJ. Lactobacilli differentially modulate expression of cytokines and maturation surface markers in murine dendritic cells. J Immunol 2002; 168: 171–178.

10. Hasselbalch H, Jeppesen DL, Engelmann MDM, Michaelsen KF, Nielsen MB. Decreased thymus size in formula-fed infants compared with breastfed infants. Acta Paediatr 1996; 85: 1029–1032.
11. Hanson LA, Korotkova M, Lundin S, Haversen L, Silfverdal SA, Mattsby-Baltzer I, et al. The transfer of immunity from mother to child. Ann N Y Acad Sci 2003; 987: 199–206.
12. Davis MK. Breastfeeding and chronic disease in childhood and adolescence. Pediatr Clin North Am 2001; 48: 125–141.
13. Gdalevich M, Mimouni D, David M, Mimouni M. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. J Am Acad Dermatol 2001; 45: 520–527.
14. Odijk J, Kull I, Borres MP, Brandtzaeg P, Edberg U, Hanson LÅ, et al. Breastfeeding and allergic disease: a multidisciplinary review of the literature (1966–2001) on the mode of early feeding in infancy and its impact on later atopic manifestations. Allergy 2003; 58: 833–843.
15. Bergmann RL, Diepgen TL, Kuss O, Bergmann KE, Kujat J, Dudenhausen JW, et al. Breastfeeding duration is a risk factor for atopic eczema. Clin Exp Allergy 2002; 32: 205–209.
16. Kramer MS, Chalmers B, Hodnett ED, Sevkovskaya Z, Dzikovich I, Shapiro S, et al. PROBIT Study Group. Promotion of Breastfeeding Intervention Trial (PROBIT): a randomized trial in the Republic of Belarus. JAMA 2001; 285: 413–420.