

PROBIOTICS IN ATOPIC DISEASE

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Plenty of epidemiological, experimental and *in vitro* evidence supports the concept that the increased prevalence of allergy, manifested in atopic eczema, allergic rhinitis and asthma, is related to reduced exposure to microbes at an early age as a result of improved public health and living conditions (the hygiene hypothesis) [1]. Simultaneously, drastic reduction of dietary bacteria, mainly in the amount of genera *Lactobacillus* and *Bifidobacterium*, has succeeded changes in methods of food production and preservation [2]. Children may thus harbour different and less protective indigenous gut microbiota than earlier.

Studies among families following an anthroposophic way of life have demonstrated that prevalence of atopic diseases in children from these families is significantly lower than in children of families not following that lifestyle [3]. Characteristics of the anthroposophic lifestyle include restrictive use of antibiotics, antipyretics and vaccinations but ample use of organic diet, often constituting vegetables spontaneously fermented by lactobacilli, and commonness of birth at home [3,4]. These specific lifestyle features have also been shown to influence to the composition of the gut microbiota suggesting the importance of the gut microbiota in the development of allergy [4]. Indeed, a Swedish study found that 2-year old allergic children were less often colonised with lactobacilli than non-allergic

children whereas the latter harboured higher counts of coliforms and *Staphylococcus aureus* [5]. Preschool and school-age Japanese children with atopic eczema were shown to have lower counts of fecal *Bifidobacterium* than healthy subjects and they were also more often colonised with *Staphylococcus* [6].

We have showed by fluorescence *in situ* hybridisation that neonates who later developed skin prick test reactivity to environmental antigens had higher counts of clostridia and lower counts of bifidobacteria in their faeces than those not going to develop such a reactivity [7]. Björkstén *et al* [8] found by bacterial culture methods that children who developed skin prick test reactivity and/or atopic eczema by the age of 2 years were less often colonised with bifidobacteria during the first year of life than those not developing these disorders. There were also differences in the colonisation of enterococci, clostridia, *Staphylococcus aureus* and *Bacteroides* [8]. These studies suggest that certain species of gut microbiota may contribute to the immune system to adopt a non-allergic mode.

Probiotics, defined as live microbial food ingredients that beneficially affect host health, most often belong to the genera *Bifidobacterium* or *Lactobacillus* [9,10]. Several species of these two genera have belonged to human diet for millennia in a form of soured food [2,9] whereas scientific interest to these bacteria arose approximately a century ago [11]. A bacterial strain must fulfil several criteria before it can be regarded as a probiotic. These include human origin, survival in the gut, ability to adhere to intestinal epithelium and to induce immune responses, safety in human use, scientifically documented beneficial effects, and invariable properties during all stages of manufacturing,

processing and preservation [9]. Moreover, all candidate probiotic strains should be closely evaluated and beneficial effects of a certain strain should not be related to any other strain without indisputable proofs [9,10].

To date, most of randomised placebo-controlled trials of probiotics in atopic disease have focused on patients with atopic eczema. Majamaa and Isolauri [12] evaluated infants with atopic eczema and cow milk allergy. All the infants were treated with an extensively hydrolysed whey formula with or without the addition of *Lactobacillus rhamnosus* GG. The clinical score of atopic eczema improved significantly during one month study period only in infants treated with the extensively hydrolysed whey formula fortified with the probiotic [12]. In parallel, concentrations of faecal markers of intestinal inflammation decreased significantly only in this group [12]. A similar effect on atopic eczema was found in a clinical trial of breast-feeding infants where extensively hydrolysed whey formula was fortified with either *Lactobacillus rhamnosus* GG or *Bifidobacterium lactis* Bb-12 [13]. Rosenfeldt et al [14] gave a combination of *Lactobacillus rhamnosus* 19070-2 and *Lactobacillus reuteri* DSM 122460 for 6 weeks to 1- to 13-year-old children with atopic eczema in a crossover study. They found the combination therapeutic especially in patients with positive skin prick test responses and increased immunoglobulin E (IgE) concentrations [14]. These authors have further demonstrated that this same combination was able to reduce small intestine permeability and ameliorate gastrointestinal symptoms in children suffering from atopic eczema [15]. Recently, *Lactobacillus* GG was shown to alleviate symptoms of atopic eczema in IgE-sensitised but not in non-IgE-sensitised infants [16]. However, there was no therapeutic effect when this same strain was

administered together with three other strains. So far, no improvements in symptoms of respiratory allergic diseases have been detected in randomised placebo-controlled clinical studies evaluating effects of lactobacilli on these disorders [17,18].

We have addressed whether probiotics might prevent early atopic disease in a randomised placebo-controlled clinical trial. *Lactobacillus rhamnosus* GG was administered perinatally to mothers and infants up to age of 6 months [19]. Children had a family history of atopic disease. The administration of the probiotic halved the development of atopic eczema during the first 2 years of life. There were no differences in IgE-mediated allergic hypersensitivity [19]. The extension of the preventive effect beyond infancy was demonstrated in the 4-year follow-up of the same study cohort [20]. Consumption of *Lactobacillus rhamnosus* GG by pregnant and lactating mothers has been shown to increase the amount of anti-inflammatory cytokine TGF- β in breast milk. The risk of atopic eczema during infancy was reduced among those whose mothers consumed the probiotic strain [21].

Experimental studies have shown that probiotics have strain-specific effects in intestinal lumen, epithelial cells and immune cells with anti-allergic potential. These studies indicate that probiotics may enhance gut luminal antigen degradation and intestinal epithelial barrier function, and induce regulatory immune responses [22]. Future studies should address more closely how probiotics operate in complex gastrointestinal ecosystem *in vivo* and how their actions are related to clinical effects in dose-dependent manner.

References

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