The Use of Probiotics in Respiratory Allergy

Gemma Vilà-Nadal¹, Elsa Phillips-Anglés¹ and Javier Domínguez-Ortega¹,²,*

¹Allergy Department; ²Institute for Health Research (IDiPAZ). Hospital Universitario La Paz., Madrid, Spain

Abstract: There is a high and steadily increasing prevalence of respiratory allergy throughout the world, especially in paediatric population and in industrialized and developing countries. A complex interplay between genetic and environmental factors has been implicated to explain this dramatic increase in prevalence of allergic diseases. It has been suggested that exposure to microbes plays a critical role in the development of the early immune system and may contribute to allergic diseases through their effect on mucosal immunity. Probiotics, microorganisms exerting beneficial effects on the host, are used in a great number of paediatric and adult diseases, mainly gastrointestinal disorders, but they have been proposed to be beneficial also in allergic diseases. Different trials have been published finding benefits in the use of probiotics in prevention and treatment of atopic dermatitis, but to date, studies have yielded inconsistent findings to support a protective association between their use on prevention of allergic rhinitis or asthma. However, probiotics may be beneficial in improving symptoms and quality of life in patients with allergic rhinitis although it remains limited due to study heterogeneity and variable outcome measures. As a result of these controversies, future investigations with a better standardization are needed. In this review, we summarize recent clinical research to elucidate the mechanisms of probiotics and their effect in respiratory allergy. According to published data, probiotics could emerge as a novel, complementary treatment option for allergic rhinitis but not for asthma.

Keywords: Probiotics, respiratory allergy, allergic rhinitis, asthma.

INTRODUCTION

Respiratory allergy affects an estimated 10 to 25% of the population and their prevalence is permanently increasing during the last three decades [1-3]. It seems to be more evident that allergy is the consequence of an interaction between genetic and environmental factors. Viruses, pollution, smoke and passive tobacco exposure, allergens or diet could play a key role in epigenetic changes, driving the immune system to an “allergic status”, specially if the exposure is early in life [4]. Microbiome includes mainly skin and mucosal bacterial flora, both aerobics and anaerobic bacteria, but also viruses and moulds, ordinary living in the same areas of the human body [5]. In later years, the focus has been placed has been placed on the intestinal microbiota which is the major source of microbial exposure, composed by 10 times the number of cells in the entire body [6]. It could interact with gut-associated lymphoid tissue and modulate immunologic and inflammatory responses [7]. After birth, the diversity of the gut microbiome increases with age [8]. A deprive microbial exposure or differences in patterns of microbial flora early in life, could change the balance of immune development contributing to explain this rapid increase in the prevalence of allergy. The disappearance of ancestral indigenous microbiota species or the loss of gut bacterial diversity has been observed in children at risk of asthma [9-11]. Prevalence of Lactobacillus in the first weeks of life [12] or the gram-negative/gram-positive ratio at 12 months of age, may affect the risk of developing allergic diseases [13, 14].

According to these findings, the role of beneficial bacteria in the form of probiotics to modify gut microbial composition has been explored. Probiotics have been used for the treatment of gastrointestinal disturbances, cardiovascular diseases, autoimmune diseases and obesity [15, 16]. For atopic diseases, there are numerous studies on the efficacy of probiotics for the prevention and treatment of atopic dermatitis [17-21]. Even the World Allergy Organization (WAO) has recently provided evidence-based recommendations suggesting the use of probiotics in pregnant women in high risk of allergy, in women who breastfeed infants at high risk of allergy and, finally, in children at high risk of developing allergies, could be net beneficial for prevention of eczema [22].

Even though a large number of studies have evaluated the efficacy of probiotics for the prevention and treatment of IgE-mediated respiratory diseases, results have been at least controversial. The aim of this review was to evaluate the effect of probiotics in the setting of prevention and treatment of respiratory allergy, allergic rhinitis and asthma, according to current published evidence.

MECHANISM OF ACTION OF PROBIOTICS IN ALLERGIC DISEASES

According to the World Health Organization and the Food and Agriculture Organization of the United

ISSN: 2223-3806 / E-ISSN: 1927-5951/16 © 2016 Lifescience Global
Nations, “probiotics are live microorganisms which, when administered in adequate amounts as part of food, confers a beneficial health effect by producing gut microflora on the host” [23]. They are usually anaerobic organisms that ferment ingested food products in the intestines to produce lactic acid. In medicine, probiotics are used as a supplementary therapeutic agent for several diseases. Probiotics may improve health by several mechanisms although its action mechanism has not been fully clarified. The mechanism of action of probiotics could be multi-faceted. The genre most commonly used in prevention and treatment of allergic diseases includes Lactobacillus and Bifidobacterium. Their biological features enable them to predominate and prevail over potential pathogenic microorganisms in the human digestive tract, by suppressing their growth or/and competing for binding sites on the intestinal mucosa. These bacteria affect T helper (TH) responses, eliciting TH1 cytokine production or, indirectly, by stimulating T-regulation [24]. They have also been implicated in actively suppressing TH2 responses. Lactobacillus bacteria affect T-regulatory cells by generating semi-mature dendritic cells and increasing the expression of CD40. Specifically, L paracasei NCC2461 inhibits Interleukin (IL)-4, IL-5 or interferon-γ while inducing specific regulatory cytokines such as transforming growth factor (TGF-β) and IL-10 [23]. Probiotics can also enhance local IgA production which affects directly the mucosal defenses [25] and they have been involved in the maturation of adaptive T-cell immunity by stimulating the production of IL-17 (which plays a role in the immune protection to extracellular bacteria) [26]. Moreover, it has been recently described that probiotics could also have a role in modifying genetic susceptibility to eczema in high risk children affecting specific Toll-like receptors genotypes [27].

ALLERGIC RHINITIS AND TREATMENT WITH PROBIOTICS

Studies have shown that probiotics may be useful in the treatment of AR (Table 1). Different strains have been studied for AR. Wassemberg et al. investigated the effect of L. paracasei ST-11 strain in a group of 31 volunteer adult patients (18-35 years) with AR due to grass pollen confirmed by either positive skin prick test or specific IgE for grass pollen [28]. They were enrolled and randomized in a DBPC study in order to receive fermented milk containing ST11 or a placebo, administered out of the pollen season, in a cross-over setting, during a period of 4 weeks. A nasal provocation test was performed with a standardized grass pollen extract and clinical parameters were compared between the two treatment periods. Subjects who received ST11-fermented milk showed improvement of subjective nasal congestion and nasal pruritus, measured by a visual analogical scale (p=0.04), in comparison to those patients under placebo. However, no significant differences were observed in allergen dose that caused a reaction or obstruction measure by peak nasal inspiratory flow [28].

Perrin et al. also studied the same probiotic L. paracasei versus a blend of L. acidophilus and B. lactis in a DBPC cross-over trial, enrolling grass pollen allergic patients (n=31) during 4 weeks, in two phases, out of the pollen season [29]. Although no effect was observed on nasal congestion, a significant reduction of nasal pruritus in the L. paracasei group was demonstrated. Moreover, leukocytes in nasal fluids and IL-5 secretion were also significantly decreased in patients under treatment with L. paracasei. Costa et al., studied, in a DBPC trial, the efficacy of the probiotic L. paracasei LP-33 in 425 patients with AR to grass pollen treated with loratadine and presenting altered quality of life [30]. After a run-in period receiving loratadine alone for 7-10 days, patients with a Rhinitis Quality of Life Questionnaire (RQLQ) ≥ 2 were randomized to placebo or LP-33 in addition to loratadine for 5 weeks. Loratadine was then discontinued and, only LP-33 or placebo, were continued for two additional weeks. The study confirmed a significant improvement in the RQLQ which was the primary end-point, in the LP-33 group (p=0.0255) and in ocular symptoms (p=0.0029). On the contrary, no significant differences were observed in nasal symptoms. Previously, two randomized DBPC trials had demonstrated improvement in the quality of life in persistent AR with the use of probiotics. In one of them, 90 house-dust mites allergic children ingested LP-33 over a period of 30 days [31], and in other similar results were obtained in 80 children [32]. Finally, a significant improvement in the total symptom score was also found for the Japanese cedar pollen allergic patients after supplementation with L. paracasei. [33].

Other strains have been explored. Lue et al showed that the use of levocetirizine plus L. johnsonii was more effective than levocetirizine alone in 63 children with perennial AR of at least one year’s duration in a randomized, open-label cross-over designed trial [34]. Both groups had improved the total symptom score from diary cards, but improvement was significantly higher in the group under the combination of antihistamine and probiotic, while no significant differences were observed in quality of life and immunological parameters between both groups. The
differences persisted 3 months after the discontinuation of probiotics. The combination of *L. acidophilus* and *B. lactis* in children (n= 47) with birch pollen AR was studied over a period of 4 months [35]. Results showed prevention in the pollen-induced infiltration of eosinophils into the nasal mucosa and a tendency towards the reduction in nasal symptoms. The role of *Escherichia coli* Strain Nissle 1917 supplementation has been recently explored in grass pollen allergic subjects with AR, but no significant effect has been shown [36]. Finally, decreased eosinophils and diminished IFN-γ in peripheral blood were reported after the ingestion of *B. longum*, thus also reducing the need for medication in Japanese cedar pollinosis [37].

*Vliagoftis et al.* in a meta-analysis published in 2008, described the results of 12 randomized clinical trials with probiotics in AR. In 9 of them, there were some improvements in clinical outcomes [38]. However, the heterogeneity of studies advised caution in the interpretation of the results. In 2015, *Zajac et al.*, have been published a systematic review and meta-analysis of probiotics for the treatment of AR [39]. A total of 23 studies with 1919 patients were identified, including 21 randomized double-blind placebo-controlled (DBPC) and 2 randomized cross-over studies. In 17 of the trials the results showed a significant clinical benefit from the use of probiotics, at least in one of the measured outcomes when compared to placebo, especially those in the field of quality of life. On the other hand, 6 showed no effect, specifically in the area of the rhinitis total symptom score. Despite including almost 2000 patients, the overall cohort remained fairly heterogeneous and there were also limitations for comparison between individual studies, specifically the variability in study designs, outcome measures and probiotic formulations tested. In spite of these shortcomings, the conclusion from this systematic review suggested that probiotics might have some beneficial effects in patients with AR according to current evidence.

## THE USE OF PROBIOTICS IN PREVENTION OF ALLERGIC RHINITIS

Even though current data shows that probiotics have a therapeutic effect in AR, no effect has been observed in relation to the prevention of the development of AR [22]. Most studies exploring the role of probiotics in atopic disease have also focused on early manifestations of respiratory allergy. *Peng et al.* have systematically reviewed them to determine the role of probiotics in prevention of AR [40]. There were five trials from which information about AR prevention could be extracted. The outcome of the meta-analysis revealed no differences in the incidence of AR between the probiotic and placebo groups (odds ratio 1.07 [95% CI, 0.81-1.42]; *p*=0.64).

## ASTHMA AND PROBIOTICS

Studies exploring the role of probiotics in AD have also focused on prevention of asthma development.
Table 2: Representative Probiotics Used to Prevent Asthma Disease. No Effect on Prevention of Asthma was Found in any of the Trials

<table>
<thead>
<tr>
<th>Probiotic</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>L. casei</td>
<td>Giovannini et al. (2007) [44]</td>
</tr>
<tr>
<td>L. rhamnosus GG, L. acidophilus La-5 and B. animalis subsp. lactis Bb-12</td>
<td>Simpson et al. (2015) [45]</td>
</tr>
<tr>
<td>B. longum (BL99.9) and L. rhamnosus (LPR)</td>
<td>Loo et al. (2014) [46]</td>
</tr>
<tr>
<td>L. acidophilus LA-5,</td>
<td>Bertelsen et al. (2014) [47]</td>
</tr>
<tr>
<td><em>Bifidobacteria and Propionibacteria</em></td>
<td>Kuitunen et al. (2009) [41]</td>
</tr>
<tr>
<td>L. reuteri</td>
<td>Abrahamsson et al. (2013) [42]</td>
</tr>
<tr>
<td>L. rhamnosus</td>
<td>Rose et al. (2010) [48]</td>
</tr>
</tbody>
</table>

L. acidophilus: Lactobacillus acidophilus; L. reuteri: Lactobacillus reuteri; L. casei: Lactobacillus casei; L. rhamnosus: Lactobacillus rhamnosus; B. longum: Bifidobacterium longum; B. lactis: Bifidobacterium lactis.

(Table 2). If probiotics are able to prevent atopic eczema, it would be expected that, treated-children in these trials would have less asthma later in life. However, results have been at the moment discouraging. In a Finnish DBPC trial, 1223 mothers with infants at high risk of allergy received a mixture of *Bifidobacterium* and *Propionibacteria* during the last months of pregnancy. Infants continued taking probiotics until the age of six months. A preventive effect on asthma was not found up to 5 years of age in the total cohort, but interestingly less IgE-allergic disease occurred in cesarean-delivered children receiving probiotics [41]. A large Swedish follow-up study (7 years) completing a DBPC trial evaluating the effect of *L. reuteri* on allergic disease and sensitization, showed that the administration of the probiotic during the last weeks of gestation and 1 year in infancy, did not lead to a lower prevalence of asthma at school age [42]. Another large study could not find a long-term effect of *Lactobacillus paracasei* F19 (LF19) on any diagnosed allergic disease. Researchers investigated the effect of LF19 during weaning, from 4-13 months of age, as a tool in primary prevention of allergic disease [43]. The intervention was completed by 171 children whereas 121 were finally assessed. However, there was no effect of LF19 on respiratory allergic disease, lung function measures or FENO at age 8-9. Moreover, Giovannini et al. showed that long-term consumption of fermented milk (12 months) containing *L. casei* (n=187, 2-5 year of age) might improve the health status of children with AR reducing the annual number of rhinitis episodes, but had no effect on asthma [44]. Furthermore, in a recent meta-analysis covering 17 randomized-controlled or quasi-controlled trials and reporting data from 4755 children, no effects were observed on wheezing or asthma [21]. No beneficial effects in prevention of asthma have been observed with other different strains and worldwide populations [45-48].

Nevertheless, it has been demonstrated that *L. salivarius* LS01 and *B. breve* BR03, alone and in combination, could slightly inhibit the growth of some clinical pathogens (*Escherichia coli* and *S. aureus*) and be able to decrease the secretion of pro-inflammatory TH2 cytokines on peripheral blood mononuclear cells of allergic asthmatics [49]. Interestingly, the combination of both strains in the same formulation seemed to implement the immunomodulatory activity of each strain alone. This data shows promising probiotic features in allergic asthma but further research is needed.

CONCLUSIONS

Probiotics appear to have beneficial therapeutic effects in AR. They may improve the overall quality of life scores and nasal symptom scores of patients with AR, but the mechanism and the duration of this effect remains unclear. By contrast, in asthma and prevention of respiratory allergy diseases, the use of probiotics cannot be advised for general population at this point according to current data. Future research is required, including long-term follow-up studies and the use of standardized criteria, in order to address the role of probiotics in respiratory allergy.

REFERENCES

The Use of Probiotics in Respiratory Allergy


Received on 12-08-2015 Accepted on 12-10-2015 Published on 29-07-2016

DOI: http://dx.doi.org/10.6000/1927-5951.2016.06.03.1


This is an open access article licensed under the terms of the Creative Commons Attribution Non-Commercial License (http://creativecommons.org/licenses/by-nc/3.0/) which permits unrestricted, non-commercial use, distribution and reproduction in any medium, provided the work is properly cited.