ASPECTS IN THE PREVENTION AND TREATMENT WITH PROBIOTICS IN ALLERGIC DISEASES

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Abstract: *The role of probiotics in the prevention and treatment of allergic diseases is controversial. The administration of probiotics has been shown to stimulate the immune response, the lack of which has been involved in the development of atopic disorders. There are reports that recommend the supplementation of probiotics to foods for the prevention and treatment of allergic diseases. Most studies reported clinical benefits in allergic rhinitis and eczema. Although, the clinical benefits of probiotic therapy depend on many factors: type of bacterium, dosing regimen, method of administration and other underlying host factors. Despite the promising evidence, the role of probiotics in allergic diseases should be further investigated as the current knowledge of the characteristics that are necessary for their functionality in the gut is not complete.*

Cuvinte cheie: *probiotice, boli alergice*

Rezumat: *Utilitatea probioticelor în prevenirea şi tratamentul bolilor alergice este controversată. S-a demonstrat că dezechilibrul florei comensale poate duce la dezvoltarea bolilor alergice şi că administrarea de probiotice stimulează răspunsul imun. Sunt studii care recomandă administrarea probioticelor în prevenţia şi tratamentul bolilor alergice. Majoritatea studiilor publicate au raportat beneficii din punct de vedere clinic, mai ales în rinita alergică şi eczemă.Totuşi beneficiile terapiei cu probiotice depind de numeroşi factori: tipul de bacterie, dozajul, metoda de administrare şi de factorii specifici gazdei. În ciuda studiilor pozitive, rolul probioticelor în bolile alergice rămâne în continuare de investigat.*

INTRODUCTION

In the recent decades, we have witnessed an alarming increase in the incidence of atopic diseases with a clear difference between the developed and developing countries. Nowadays, it is estimated that 20% of the global population is suffering from some form of allergic disease with a rising prevalence.(1) The exact etiology of allergic diseases is still confusing, many researchers have suggested that environmental exposures may be indispensable trigger factors in the patogeny of allergic diseases. In industrialized countries, there was a bigger increase in the prevalence of allergic disorders and that determined the researchers to formulate the hygiene hypothesis trying to explain the etiopathogeny of the disease. The hygiene hypothesis explains that limited childhood exposure to bacterial and viral pathogens would affect the balance between T-helper(Th) cells by favouring the Th2 phenotype of the immune system.(2) If the stimulation of Th1 cells is insufficient this cannot prevent the expansion of Th2 cells and that leads to the predisposition to allergy.(2) Over the same period of time, there has also been an increase in the incidence of diseases that are characterized by a predominantly Th1-polarized T-cell response. This suggests that immunoregulatory mechanisms capable of controlling both Th1 and Th2 responses do not fully mature in the relative absence of microbial stimuli. While most of research has focused on early exposure to infectious agents, it is recognized that commensal bacteria, which provide the first and major source of microbial exposure, play a central part not only in Th1/Th2 polarization but also in inducing the appropriate regulatory mechanisms. One of the reasons for allergic reactions is a late colonization of Bifidobacterium and Lactobacillus spp. in the gastrointestinal tract of children.(3) The difference in gastrointestinal microbiota may play a role in susceptibility to allergy. There is evidence that the composition of commensal bacteria differs between children who develop atopic diseases and those who do not, and between children from countries with a high or low incidence of atopic disease.(4) Allergic disorders are related to change of the Th1/Th2 cytokine balance into a Th2 response. This leads to the activation of Th2 cytokines and the release of interleukin-4 (IL-4), IL-5, and IL-13.This release leads to the production of immunoglobulin E(IgE). The IgE in turn interacts with basophils resulting in their degranulation and release of histamines, prostaglandins, chemokines and cytokines leading to smooth muscle contraction, increased vascular permeability, recruitment of more Th2 cells and eosinophils and release of neuropeptides. Probiotics can potentially activate the dendritic cells and the Th1 response leading to suppress Th2 responses. Pediatric studies conclude that probiotic use in children with atopic conditions(atopic dermatitis) results in amplifying of interferon(IFN)-production and decrease IgE, IL-5, and IL-10 secretion.(5)

The hypothesis that probiotics might influence immunity by altering specific immune parameters, thus playing beneficial roles in human diseases is of great interest. In fact, probiotics:

- can modulate and stabilize the composition of the microbiota and, therefore, may have immunomodulatory effects;
- are able to inhibit the inflammatory response of the intestinal immune system through inhibition of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) activation or in combination with an anti-apoptotic action on intestinal epithelial cells;
- are able to increase the activity of natural killer(NK) cells, which are first line of defence as they can perform cytotoxic

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activities independent from prior sensitization to antigens;
- increase the secretion of mucus;
- may have a direct immunomodulatory action: after being captured in the Peyer's patches, they can induce the secretion of cytokines and the expression of co-stimulatory molecules by antigen presenting cells (APC);
- some strains of lactobacilli induce dendritic cells (DC) maturation

With a targeted use of specific probiotic strains, it is possible to induce an immune stimulant type of response on both B (increase of humoral immunity) and T lymphocytes (increase of cell-mediated immunity) and on the phagocytic component, particularly on polymorphonuclear cells. The gastrointestinal tract represents an important interface between host and environment and, has the dual role of excluding pathogens while facilitating the absorption of nutrients. Commensal bacteria participate in both tasks of the gastrointestinal tract: some of them help in the absorption of otherwise indigestible nutrients, and some of them are contributing to colonization resistance, that is the ability to inhibit colonization or overgrowth of potentially pathogenic microorganisms, by producing antimicrobial substances, and stimulating the immune system.

Atopic dermatitis. The role of probiotics in prevention and therapy of atopic dermatitis has been increasingly studied. The prevention of allergic disorders is best on preventing sensitization to an offending allergen. The prevention of the allergy has been of great help when assessing atopic eczema, the most prevalent allergic disease in childhood. More than half of the published studies demonstrate a decrease in eczema prevalence until 2 years.(6) Effects have been most consistent with combined prenatal and direct postnatal supplementation of the infant and appear strain-specific, with Lactobacillus rhamnosus most often showing an effect. Prenatal-only and postnatal-only studies often fail to show effects.(7) The present data demonstrate that when the right probiotic strains are selected and used in defined settings with symptoms of food and intestinal origin, there are excellent possibilities for both primary and secondary prevention of atopic eczema and also prevention of sensitization.

Food Allergies. Food allergies are considered to be central in the pathogenesis of AD,and if we target the enteric mucosa, the primary route of food antigen contact and sensitization, with probiotics might influence complex mechanisms. The interest in modulating commensal bacterial flora with prebiotics and probiotics to prevent and treat food allergy has multiplied in recent years. Modulation of commensal bacteria of the gut with probiotics has been shown to modulate the immune system and positively affect both the prevention and treatment of food allergy There have also been several published studies showing that oral administration of Bfdbm or Lctbs strains could alleviate the food allergy.(8) The effects have been highly variable depending on the mode of treatment, and even though the literature is promising, the optimal treatment remains to be established.

Allergic rhinitis. Studies on the efficacy of probiotics in preventing and treating allergic rhinitis are confusing. In one study, administration of *L. casei Shirota* (LcS) in participants with allergic rhinitis resulted in a significant reduction in antigen-induced interleukin (IL)-5, IL-6, and interferon gamma production associated with an increase in specific immunoglobulin G and a decrease in IgE levels. The majority of the trials revealed a decrease in symptom severity and a low use of relief medications. One study suggested that fermented milk containing *Lctbs casei* strain *Shirota* does not prevent allergic symptoms although the addition of the strain may delay the occurrence of allergic symptoms in patients with moderate-to-severe nasal symptoms.(9)

Asthma. The efficacy of probiotics supplementation in the treatment of asthma has been considered in a small number of studies. The studies have mainly focused on the treatment rather than prevention of asthma. The researchers found no statistical difference between intervention and control groups of asthmatic children. The number of rhinitis episodes was lower in the probiotic group leading the authors to conclude that *Lactobacillus casei* may benefit children with allergic rhinitis but not asthmatic children.(5) The trials of the effects of probiotics on asthma are few and show irrelevant results, so that a conclusion regarding the benefits of probiotics cannot yet be reached although some positive experiments on animals suggests the need for further investigations.

Conclusions:

The role of probiotics for the prevention and treatment of allergic diseases is controversial. The trials vary in study design, including probiotics strains, or time (postnatal/prenatal) and period of probiotics supplementation, thereby the comparability of the results is limited. Combining probiotics with prebiotics or using probiotics mixed might play a role in confusing the results of most of the studies. Host factors (genetic differences and allergic predisposition) and other environmental factors like individual microbiota, diet (including consumption of prebiotics) and treatment with antibiotics are other important factors that can change results. Better understanding of the mechanisms of the heterogeneous manifestations of atopic disease, discovering all the effects of different probiotic strains are essential in validation of specific strains with anti-allergic potential. Research activities are focused on identification of specific probiotic strains with immunomodulatory potential and on how dietary content interacts with the most efficacious probiotic strains. Selection of the most beneficial probiotic strain, the dose and the timing of supplementation still need to be determined.

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