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Probiotics effect in prevention and treatment of atopic dermatitis and eczema in children

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Abstract

The composition of the intestinal microbiota plays an important role in the occurrence of allergies. Based on the immunomodulating capabilities of bacteria, various studies have investigated the potential role of probiotics in the prevention of eczema and atopic dermatitis in children.

Atopic dermatitis (AD) is one of the first manifestations in the evolution of allergies, with a continuously increasing incidence worldwide. In the literature, various risk factors are described to play a role in the occurrence of DA, but the actual cause of the disease is still unknown. The intestinal flora seems to be involved in the development of AD, as patients with AD show quantitative, qualitative and functional changes. An imbalance of the human gut microbiota in the first years of life is a possible risk factor for immune-mediated disorders such as allergies. With the aim of modulating the gut microbiota, probiotic supplementation in the first months of life has been used to prevent allergic diseases in infants, with variable success. However, not much is known about the long-term consequences of the use of probiotics in the newborn on the composition of the gut microbiota. The aim of this paper is to highlight the positive links between the use of probiotics and the prevention or cure of eczema and atopic dermatitis.

Keywords: probiotics, eczema, atopic dermatitis, intestinal microbiota, prevention, healing, Scoring Atopic Dermatitis (SCORAD)

INTRODUCTION

Up to 40% of the US and European populations suffer from at least one type of allergy, and the prevalence of allergies is on the rise. Among them, eczema is one of childhood's most common inflammatory skin diseases. The etiology of allergic diseases is unknown, although it has been well-established that both genetic and environmental factors play a role. There is increasing evidence that gut microbiota is a crucial factor in the development of allergic diseases. The development of allergies has been linked to reduced microbial exposure in early childhood, reduced bacterial diversity and

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altered gut microbiota composition [1,2,3]. In this context, the perinatal period is the opportune period for influencing the composition of the intestinal microbiota and possibly modulating the development of allergic diseases [4].

Atopic dermatitis and allergic diseases significantly increase morbidity in childhood, and the prevalence of allergic diseases has increased in recent decades. The prevalence of atopic dermatitis has increased in last decades between 2-fold to 3-fold. In approximately 60% of cases, the disease manifests in the first year of life. The evolution may be continuous for long periods or may be recurrent. AD is mild in most of the cases [5]. This generates the development of strategies to prevent allergic diseases. The excessive hygiene hypothesis suggests that the increased prevalence of allergic diseases in children is associated with reduced exposure to microbial components early in life [6]. Differences in the intestinal microbiota between allergic and nonallergic children have been described, which precede the development of allergic disease suggesting a potential causal relationship [7,8]. Based on this hypothesis, primary and tertiary prevention of allergic diseases could be achieved by administration of appropriate bacteria [9].

The mechanisms by which probiotic bacteria could induce a beneficial effect in the prevention of allergic diseases remain to be elucidated. Probiotic bacteria can act at three levels: modification of the intestinal microbiota, fortifying the mucosal barrier, and immunomodulation [10]. Each strain of probiotics has its own unique immunomodulatory activity in vitro. This may also be true for their clinical use. It was hypothesized that targeted selected strains might have more potential to target specific diseases such as allergic diseases [9].

IMMUNOMODULATORY EFFECTS OF PROBIOTICS

Administration of probiotics in adequate amounts confers a health benefit to the host, and has been shown to be able to reduce the incidence of atopic dermatitis, cow's milk allergy and the severity of allergic manifestations [11,12]. The first landmark work studying probiotics used Lactobacillus rhamnosus GG, which was supplemented to mothers prenatally and subsequently, 6 months after birth, to infants [9]. This study proved that administrating this probiotic is associated with a significant reduction in the cumulative incidence of eczema in the first 7 years of life [13,14]. A number of other studies also show the preventive effects of probiotics on the onset of eczema [9,15-17]. However, there is no proven "generic" benefit common to all probiotics. Therefore, a Cochrane review on this topic concluded that there is insufficient evidence to recommend the addition of probiotics to infant food for the prevention of allergic disease or food hypersensitivity [17].

Regarding the management of atopic dermatitis with the help of probiotics, it shows no effect or only a modest effect. However, recent studies show promising results [5,18-20].

A reduction in overall diversity, a reduced abundance of commensal bacteria and an increased abundance of potentially pathogenic bacteria in the gut microbiota has been associated with the development of immune-mediated disorders later in life. Data from observational studies are conflicting, exemplified by a recent study showing a more diverse microbiota in children with eczema [21] and no taxa that promote or protect clear allergies, in contrast to another study revealing that high diversity of the total microbiota and high abundance of butyrate-producing bacteria are inversely associated with the severity of atopic eczema [22]. More, there is an ongoing debate about whether in the development of allergy an altered diversity of the gut microbiota is more important than the altered prevalence of certain bacterial species [23].

Representative species and strains of lactobacilli and bifidobacteria have been used as probiotics with the aim of colonizing the infant's gut and modulating the host's immune response. Several studies have indeed shown the benefits of probiotic treatment in atopic children and thus modulation of the infant's gut microbiota [24-26] even by exclusive maternal provision during late pregnancy [27]. Meta-analyses provide evidence in support of a moderate role of probiotics in the prevention of atopic dermatitis and IgE-associated atopic dermatitis in infants, [28] but more heterogeneous results are found for probiotic supplementation in the treatment of eczema [29]. Strain specificity and the role of the timing of probiotic administration is of particular importance, as some studies have shown no beneficial effect on the prevention of eczema after probiotic supplementation [21,30,31]. Therefore, it seems essential to administer probiotics during pregnancy and in the first months of

life to be able to reasonably assess the effects of this intervention on the microbial colonization of the gut and possible immunological effects [32].

DA is now thought to result from a disturbed T-helper Th1/Th2 balance, and the condition is often accompanied by impaired skin barrier function and high levels of total or allergen-specific serum IgE. Repair of the epidermal barrier has previously been shown to be key to the treatment of AD and the use of emollients in skin care is recommended for children affected by AD.

In addition, glucocorticoids or calcineurin inhibitors are often prescribed along with non-specific immunosuppressive drugs for patients with severe conditions depending on the lesions and their location. Microbial colonization was found in more than 90% of DA lesions [32]. The presence of an imbalance of skin and intestinal flora in AD patients has been identified, and evidence from animal experiments demonstrates that altered intestinal flora can induce and aggravate dermatitis, such as AD, characterized by Th2 and Th17 immune responses [33]. Previous studies have demonstrated the utility of probiotics, live microorganisms that are beneficial to host health, for the treatment and prevention of AD [34]. Probiotics are thought to inhibit Th2-mediated immune imbalance by regulating allergic reactions [35]. Medical probiotics can be classified into different genera, species, and strains, and have effects that are specific and strain-dependent, so effects seen with one type of probiotic strain treatment cannot be generalized to others. Beneficial microorganisms alone or in combination with other strains have specific preventive and curative effects that may be related to interactions with the immune regulatory system [36-38].

Lactobacillus is known to reduce the pro-inflammatory response by regulating nuclear factor kappa B (NF-jB) signaling. Probiotics may contribute to the maturation of dendritic cells (DCs) to allow the production of interleukins or other anti-inflammatory cytokines such as interleukins (IL)-10. In addition, probiotics can induce the response of human monocyte-derived CDs to produce IL-10, and then could trigger the polarization and survival of regulatory T cells (Tregs). Bifidobacterium is identified to be associated with the induction of interferon-gamma (IFN-c) and tumor necrosis factor-alpha (TNF-a) released by CD, and Bifidobacterium bifidum is also linked to the activation of Th17 cells through the release of IL. -17. In addition, numerous researchers have reported the actions of probiotics in regulating the Th1/Th2 balance and preventing inflammatory skin diseases such as AD [38,39].

THE PROTECTIVE EFFECT OF PROBIOTICS DURING PREGNANCY AND IN THE FIRST MONTHS OF LIFE

Probiotics have a protective effect only especially when administered during pregnancy and then after birth, according to existing studies. Probiotic treatment is effective and independent of the use of a single lactobacillus strain or a combination of different probiotic bacterial strains if administered as such. Probiotic treatment has been shown to be effective for the primary prevention of AD both in the general population and in populations at high risk for AD [40].

been shown to play an important role in regulating immune function, especially for infants and young children, whose gut flora is not yet mature and is more easily influenced by complex environmental factors, including diet and antibiotics. Probiotics are often used and effective for restoring intestinal microbial function, especially strains of Lactobacillus and Bifidobacterium.

A good therapeutic effect on DA is a mixture of these two bacteria. However, the basic mechanisms underlying these effects remain unclear. The therapeutic mechanisms of probiotics on atopic diseases or allergies may be attributed to the regulation of the immune system, competitive suppression of invading microbes, modification of pathogenic toxins or host products, and improvement of skin barrier function [41].

A high degree of inter-individual variation should be taken into account when discussing the impact of probiotics on patients. For example, one study showed that the effect of probiotic consumption was closely associated with the status of an individual's basal gut microbiota, and a healthy gut microbiota could contribute to the ultimate effect of the probiotic [42].

This result takes into account the fact that intestinal persistence of probiotics is based on many factors, such as resistance to colonization, production of short-chain fatty acids, competitive exclusion of pathogens and bacteriocin release [43,44].

Primary prevention of eczema and atopic dermatitis by perinatal administration of probiotic bacteria indeed

involves modulating the early colonization of the gut microbiota, which may result in modulating the development and maturation of the infant's immune system. Modulation of the immune response by interaction with intestinal dendritic cells with subsequent effects on T cell differentiation and induction of regulatory T cells has been suggested [45].

In addition, recognition of commensal bacteria by TLRs (toll-like receptors) on intestinal epithelial cells is essential for intestinal (immune) homeostasis [46,47]. Probiotic signaling through TLRs may contribute to maintaining intestinal mucosal homeostasis and thus preventing eczema [9].

DISCUSSION

The development and maturation of the gut microbiota is a dynamic and non-random process in which positive and negative interactions between key microbes occur. This process is influenced by many perinatal conditions, such as the mode of delivery, the type of feeding, and the use of antibiotics.

The microbiological profile of the gastrointestinal tract of exclusively breastfed infants is different from that of formula- or formula-fed infants. The number of Lactobacilli is higher in breastfed infants than in formula-fed infants. The microbiological profile of the digestive tract of newborns using exclusively formula can promote the development of allergic reactions, autoimmune diseases, and many other disease entities [48].

In addition, breastfeeding appears to moderate the deleterious effects of cesarean delivery and intrapartum antibiotics on the early microbiota, producing a microbiota profile more similar to that of vaginally delivered infants or those not receiving antibiotics [49]. Exclusive breastfeeding is essential in the first months of life [48].

Probiotics have immunomodulatory effects and clinical benefits, being promising in the treatment of various diseases, in case of appropriate administration [50,51]. Probiotics exert their positive effects on health by changing the composition of the intestinal microbiome and increasing the number of Bifidobacterium and Lactobacillus species [52].

Therefore, by protecting against colonization with pathogenic bacteria, probiotics enhance the intestinal barrier and reduce the risk of developing AD [53].

Pre- and postnatal probiotic supplementation reduced the incidence of AD in infants and children if they were exposed to probiotics in utero and up to 6 months after birth [54]. The study published by de Andrade PDSMA in 2022 [19] aimed to investigate the efficacy of a probiotic mixture in improving Severity Scoring of Atopic Dermatitis (SCORAD) in children and adolescents with AD. Secondary outcomes were assessment of topical and oral medication use (standard treatment), the role of probiotics on sensitization (serum IgE level and skin test), and inflammation (IFN-g, IL-1b, IL-4, IL-). 6, IL-8, IL-17 and TNF-a) and tolerance (IL-10 and TGF-b) [19].

It has been suggested that neonates who develop AD later in life show delayed postnatal maturation of cellular immune functions [55]. Development of high-risk children with the atopic disease in the first year of life was correlated with a Th2 cytokine profile characterized by high levels of IL-4, IL-5 and IL-13 in the first 6 months [56]. Other reports have identified poorer neonatal responses to IFN-g and reduced capacity to produce IFN-g in the infant as a marker of the atopic phenotype [57,58]. Selected strains of probiotic bacteria administered orally during the neonatal period and childhood can potentially modulate immune responses that trigger disorders such as atopic dermatitis and eczema [59].

Currently, there are data to compare probiotic action between children and adults; this area deserves future exploration.

Potential risks of probiotic administration have been reported in studies, consisting of systemic infections, metabolic disturbances, excessive immune response in susceptible individuals, and gastrointestinal side effects. More research is needed to accurately describe the incidence and severity of adverse events related to the administration of probiotics [60,61].

QUALITY OF LIFE FOR PATIENTS WITH ATOPIC DERMATITIS AND THEIR FAMILIES

Chronic childhood diseases, such as AD, can have a negative impact on social integration, personal development and emotional state, of the quality of life of patients and their parents.

Itching, sleep disturbances, and emotional distress were the most commonly reported aspects of quality of life,

and their reporting increased with increasing disease severity. The greater severity of atopic dermatitis leads to a poorer quality of life for the child. Symptoms such as itching and excessive scratching can consequently aggravate already existing atopic dermatitis lesions, leading to significant sleep deprivation, exhaustion, emotional instability and functional impairment. The quality of life of caregivers is affected by multiple factors and may be directly affected by the quality of life of their children rather than the severity of the illness. Treatment strategies targeting the specific symptoms of atopic dermatitis should improve patient and caregiver quality of life.

Tools designed to assess patients' quality of life provide an additional level of understanding of the patient's condition and allow a standardized longitudinal assessment of therapeutic effects. The multidisciplinary approach, including participation in support groups, can lead to an improved understanding of the disease and therefore improve the quality of life. Further development and evaluation of more practical QoL scales to explore treatment efficacy, as well as additional support strategies for pediatric patients and their families, are needed [62].

CONCLUSIONS

To better understand the management of such a complex condition as atopic dermatitis (AD), with a major impact not only on patients but also on their families, further studies are still needed on the use of probiotics and/or prebiotics in the treatment ¬of children diagnosed with AD. The main challenge is the great heterogeneity of the published studies. Among these, some compare probiotics with prebiotics as single or combination therapy, as well as single strain versus probiotic strain mixtures. Briefly, the most studied probiotics were strains of Lactobacilli and Bifidobacteria. The SCORAD index was used to measure treatment effectiveness. Most studies compared their results with a placebo group and efficacy when observed in moderate to severe forms of AD in patients with other allergic diseases present. However, the results are difficult ¬to interpret because in many studies the authors suggest that the disease may tend to improve over time in some groups of patients. More studies are needed, on a more heterogenous population, on different continents.

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