

ROLE OF PROBIOTICS, PREBIOTICS AND SYNBIOTICS IN ATOPIC DERMATITIS

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ABSTRACT

Atopic dermatitis (AD) is a chronic recurrent skin disease, causing itching, with a characteristic distribution of lesions. Giving a combination of probiotics for 8 weeks to children with atopic dermatitis resulted in relieving symptoms based on Scoring Atopic Dermatitis (SCORAD) index, decrease in IgE serum levels, interleukin (IL)-5, IL-6 and interferon γ compared to placebo group. While prebiotics have potential to promote the growth of various microflora in colon. Change in microflora are given an allergic protective effect by modulating postnatal immune development. Synbiotic approach the capacity synergy between probiotics and prebiotics. Synbiotic therapy is a promising therapy for AD

Keywords: *probiotics, prebiotics, symbiotic, atopic dermatitis*

ABSTRAK

Dermatitis atopik (DA) merupakan penyakit kulit kronik residif, menimbulkan rasa gatal, dengan distribusi lesi yang khas. Pemberian kombinasi probiotik selama 8 minggu pada anak yang menderita dermatitis atopi menghasilkan penurunan gejala dermatitis berdasarkan *Scoring Atopic Dermatitis (SCORAD) index*, penurunan kadar IgE serum, interleukin (IL)-5, IL-6 dan interferon γ secara bermakna dibandingkan kelompok plasebo. Sedangkan prebiotik memiliki potensi untuk menciptakan kondisi kaya nutrisi lingkungan usus dimana mikroflora dapat berkembang. Perubahan mikroflora dikatakan dapat memberikan efek protektif alergi melalui modulasi perkembangan imun postnatal. Sinbiotik memiliki arti potensi yang sinergi antara probiotik dengan prebiotik. Dikatakan terapi sinbiotik merupakan terapi yang menjanjikan untuk DA.

Kata Kunci: Probiotik, Prebiotik, Sinbiotik, Dermatitis Atopik

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INTRODUCTION

Atopic Dermatitis (AD) is a inflammatory skin disease that influenced by hereditary and environmental factors.¹ Worldwide, developed and developing countries are facing the increase in incidence and degree of AD. Corticosteroid treatment has been shown a good results, but flares can occur and local side effects are common, such as skin atrophy. These side effects often cause fear in parents and can lead to non-compliance. Probiotics, prebiotics and synbiotics are the innovative prevention and treatment strategy for AD, which aims to manipulate the intestinal flora.²

ATOPIC DERMATITIS

Atopic dermatitis is a chronic recurrent skin disease, causing itching, with a characteristic distribution of lesions, and occurs mostly in children, but also can be occurs in adults. AD is often associated with elevated serum immunoglobulin (Ig) E levels and history of atopy.³

AD is common in infants and children. More than 85% of AD begins on the age of less than 5 years, while the prevalence in adults is only about 1-3%. The estimated prevalence of AD in United States in 10-12% in children and 0.9% in adults . Spontaneous remission can occur in 70% children before adulthood. AD is more

frequent in woman than men, with ratio 1.5:1 .⁴

ETIOLOGY AND PATHOGENESIS OF ATOPIC DERMATITIS

Several studies have shown the pathogenesis of AD is an interaction between genetic disorders, skin barrier disorders and immunologic disorders which are also influenced by environmental factors and stress. More recently, what are considered as primary are genetic mutations in the skin barrier and immune system disorders, including innate and adaptive⁵

Skin barrier dysfunction caused by mutations in keratin cytoskeleton genes, eg filaggrin gene (FLG). Chromosome 1q21, which is the location of FLG, there is also an epidermal differentiation complex (EDC) which function in the termination of epidermal differentiation. FLG is the main susceptibility gene for AD and encodes profilaggrin, which is an important protein for skin barrier formation and hydration, and plays a role in the ability of the stratum corneum to bind water. FLG mutations are found in approximately 50% of AD patients. FLG mutations are found in approximately 50% of AD patients. In addition to FLG in the skin barrier, there are also other protein disfunctions, which complementary and cause skin barrier

dysfunction. Damaged skin barrier will facilitate the entry of allergens and microbial colonization on the AD skin. Microbes trigger the formation of pro-inflammatory cytokines, causing skin inflammation. Scratching and microbial toxins will also trigger the formation of pro-inflammatory cytokines and chemokines, and adhesion molecules resulting in increased inflammatory reactions.⁵

Type I hypersensitivity (IgE mediated) and type IV (delayed type hypersensitivity) or cellular hypersensitivity play a role in the pathogenesis of AD, including Th-1 & Th-2 imbalances. In the acute phase, Th-2 cells play a role, and in the chronic phase are mediated by Th-1, and will develop into an autoimmune disease in the presence of IgE reactions to autologous epidermal proteins accompanied by the role of Th-17 cells. Th-2 cells secrete IL-3, IL-4, IL-5, IL-9, IL-13, while Th-1 secrete IFN- γ , *granulocyte - macrophage colony stimulating factor* (CSF), and IL-12.⁵

DIAGNOSTIC CRITERIA FOR ATOPIC DERMATITIS

Establishing a diagnosis of AD is often not easy. Many guidelines have been developed to help establish the diagnosis. Diagnosis is based on disease history (patient/family) and typical signs and symptoms. Chronic pruritus, and age-specific morphology and

distribution of skin lesions are important features of AD.⁵

Hanifin and Rajka are is of the guidelines for the diagnosis of AD. There are 4 major criteria and several minor criteria. The diagnosis of AD should be at least 3 major criteria and 3 minor criteria.⁵

MANAGEMENT OF ATOPIC DERMATITIS

AD management guidelines refer to the 2002-2003 international consensus on AD, the European consensus AD guideline, and the Asia Pacific version of the AD management guide. Based on these consensuses, AD management concept is to improve the skin barrier, reduce inflammation, reduce pruritus, avoid triggers of AD and provide information, education and counseling.⁵

Improves skin barrier with emollients. Emollients have been shown to be effective in repairing skin barrier. It can reduce transepidermal water loss (TEWL) and increase the skin's water storage capacity (skin water capacity). It should be applied immediately after bathing. It helps reduce the need for anti-inflammatory drugs.⁵

Inflammation can be suppressed by applying topical corticosteroids and/or topical calcineurin inhibitor. As a topical anti-inflammatory, corticosteroids have been approved for use in AD. Topical

corticosteroids are first-line drugs in moderate and severe AD. Corticosteroids are able to reduce skin barrier dysfunction, as well as their ability to reduce pruritus⁵

PROBIOTICS

According to the Food and Agriculture Organization (FAO) and World Health Organization (WHO) in 2002, probiotics are defined as live microorganisms that when administered to the host in sufficient quantities can provide health benefits.⁶

BENEFITS OF PROBIOTICS

The benefits of probiotics in humans can be divided into several categories based on their mechanism of action, including microbiological functions, nutritional functions, physiological functions and immunological functions. The microbiological function of probiotics is to prevent the attachment or invasion of pathological agents in the host body. Probiotics play a role in occupying the area or environment of the pathological agent directly by producing bacteriostatic or bactericidal substances. Some probiotics have the ability to synthesize a number of nutrients such as biotin, folate, nicotinic acid and thiamine that are beneficial for the body. Probiotics are also known to affect the body's physiology and provide benefits to the host, such as increasing the absorption of ions by gastrointestinal

epithelial cells and reducing toxicity due to bile salts.¹

THE ROLE OF PROBIOTICS

Multiple evidences have shown that prenatal and early postnatal external exposures influence genetic expression and susceptibility to disease. Microflora is first introduced into the child's digestive tract from the mother at the time of vaginal delivery and external influences such as the use of antibiotics during pregnancy. The correlation between probiotics and the immune system is thought to be through the ability of probiotics to adhere to the surface of intestinal epithelial cells and their ability to stabilize intestinal microflora, probiotics play an important role in the regulation of intestinal and systemic immunity.⁷

Adhesion of probiotics, especially lactic acid bacteria, to the intestinal epithelial wall accelerates the introduction of these bacteria to Peyer plaques which then activates dendritic proliferation. The mechanism of probiotics in AD is to work on skin barrier dysfunction, where *Lactobacillus paracasei* accelerates the restoration of skin barrier function. Probiotics work by inhibiting the development of the Th 2 immune responses, thereby reducing levels of IL4, IL5, IL6, IL9, IL10 dan IL13, thereby reducing the production of IgE and eosinofil. The decrease in IgE levels is thought to be due

to an increase in the ratio of IFN- γ and IL-4. A cytokines that plays a role in Th 1 stimulation, IFN- γ will suppress the Th 2 immune responses by reducing IL-4 synthesis.⁸

Some probiotics are also known to directly affect B cell activity and increase the humoral immune system in the form of IgA which plays a role in increasing the immunity of the gastrointestinal mucosa. The role of probiotics in the development of the immune system reinforces the 'hygiene hypothesis' theory. The hygiene hypothesis explains that reduced gastrointestinal exposure to microbiological antigens in early life can lead to immune disorders that lead to atopy.⁸

The close relationship between intestinal microflora and the development of the immune system, especially in maintaining the balance of Th-1 and Th-2 responses, is the rationale for giving probiotic supplements to prevent or treat allergic and atopic disease.⁸

PROBIOTICS IN ATOPIC DERMATITIS

The role of probiotics in preventing allergic skin diseases has been supported by several studies. Analysis of children's feces and their relationship to atopy disease showed that low numbers of *Bifidobacterium* (probiotics) and *Clostridium* in feces were associated with the incidence of dermatitis in children.⁹

A meta-analysis of randomized Clinical Trials (RCTs) published in 2012 to assess the benefit of probiotic supplementation in pregnant woman or children in preventing atopic disease has shown a reduction in the incidence of atopic dermatitis and IgE associated atopic dermatitis by about 20% in children who are in early childhood life or prenatal period.¹⁰

Research related to the role of probiotics as a therapy for atopic diseases has shown different results. Some studies show a real benefit of probiotics in reducing symptoms, while other studies show no significant benefits.¹¹

Administration combination of probiotics *Bifidobacterium bifidum*, *Lactobacillus acidophilus*, *Lactobacillus casei* and *Lactobacillus salivarius* for 8 weeks in children with atopic dermatitis resulted in a decrease in dermatitis symptoms based on the Atopic Dermatitis Scoring (SCORAD) index, decreased serum IgE levels, IL-5, IL-6 and interferon significantly compared to the placebo group.¹²

A study that assessed the effectiveness of several probiotics such as *Lactobacillus sp.* and *Bifidobacterium sp.* support the administration of probiotics as adjuvant therapy to treat atopic dermatitis. Most of the literature reviewed showed a significant benefit of probiotics in atopic dermatitis, especially in improving

inflammatory parameters, although there was no evidence of the effectiveness of probiotics in reducing the severity of symptoms.¹³

Lactobacillus rhamnosus GG (LGG) and *Bifidobacteria sp* are the most studied types of probiotics for their benefits for treating atopic dermatitis in children. In the literature study, the most frequent dose of probiotics for pediatric atopic dermatitis patients was 5×10^9 CFU (Colony Forming Unit) for 8 weeks, the lowest was 10^8 CFU and the highest 10^{10} CFU.¹³

Wu et al in 2012, showed that multiprobiotics was more effective than single probiotics. Probiotics were used in this study using probiotics containing 7 strains, *Lactobasillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactobacillus lactis*, *bifidobacterium longum*, *bifidobacterium lactis*, *bifidobacterium infantis*, *maltodreksin* and *rice starch*.¹⁴

SAFETY

Probiotics have been used in food and dairy products for a long time. In 2011, a report was released by *Agency for Healthcare Research and Quality (AHRQ)* reviewing 677 studies on the safety of using probiotics showed that there were no significant side effects. Another controlled trials did not monitor routinely for such infections and

primarily reported on gastrointestinal adverse events.^{15,16}

Some side effects of using probiotics in children have been reported, gastrointestinal symptoms, such as abdominal cramping, nausea, soft stool or flatulence; septicemia due to *Bifidobacterium* in children with omfalocoele, gene transfer that causes resistance of pathogenic bacteria to antibiotics. In addition, it is also known that the side effects of probiotics are often found in patients with immunodeficiency.¹⁷

There are several contraindications in giving probiotics because probiotics are live microorganisms, so there is a possibility that these preparations can cause pathological infections, especially in immunocompromised patients. Probiotics are not recommended in patients with serious medical conditions such as in patients with severe immunosuppression, pancreatitis, ICU patients, children with bowel syndrome or patients with open wounds after surgery. *Lactobacillus* preparations are contraindicated in patients with lactose or milk hypersensitivity, whereas *S. baulardii* is contraindicated in patient with yeast allergy.^{15,16}

Probiotics have no contraindications when given with others supplements. However, there are instructions for using probiotics. If you are taking antibiotics or

antifungal, it is better to take probiotics at different times.^{15,16}

PREBIOTICS

The concept of prebiotics was first introduced in 1995 by Glenn Gibson and Marcel Roberfroid. Prebiotic are described as “non-digestible food components that have beneficial effects on the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, thereby improving the host health.”^{18,19}

Prebiotics are substances that can encourage the growth of certain bacteria in the intestines. The following criteria are used to classify a compound as a prebiotic: (1) it should be resistant to acidic pH of stomach, cannot be hydrolyzed by mammalian enzymes, and also should not be absorbed in the gastrointestinal tract, (2) it can be fermented by gut microbiota, and (3) the growth and/or activity of the intestinal bacteria can be selectively stimulated by this compound and this process improves host health. Prebiotics contain galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) which normally target the activity of *Lactobacillus* and *Bifidobacterium*.^{18,19}

ROLE OF PREBIOTICS

In individuals who are prone to allergies, there is a lack of healthy intestinal microflora, so a new treatment strategy is

needed, which involves the provision of prebiotic supplementation. Prebiotics can be found in foods or supplements that contain indigestible ingredients that selectively stimulate the growth and/or activity of non-pathogenic gut bacteria. Prebiotics have the potential to create a nutrient-rich environment in the gut in which microflora can thrive. Changes in the microflora can provide an allergic protective effect by modulating postnatal immune development.^{20,21,22}

Prebiotics are often in the form of oligosaccharides. It may occur naturally in high amounts in breast milk or can be added as a dietary supplement to foods, beverages and infant formula. Dietary fiber and inulin, found in certain vegetables can also be classified as prebiotics.^{20,23}

A recent meta-analysis conducted by Osborn and Sinn in 2013, analyzed 4 studies which analyzed prebiotics for allergic prevention. The study said that there was a significant reduction in eczema with administration of *galactooligosaccharide* combine with *fructooligosaccharide*. Infants who are at risk of atopy who are given prebiotic supplements in the first 6 months of life have a significant reduction in the incidence of AD.^{24,25}

There are no extensive studies on the role of prebiotics in the management of AD. One small RCT did find that prebiotics

alone lowered the SCORAD index in children with AD. Overall, however, still minimal evidence of prebiotics as the standard single therapy.²⁰

SYNBIOTICS

Combinations of prebiotics and probiotics, known as synbiotics, appear to hold promise for treating AD. This term should be used to describe products in which prebiotic compounds selectively stimulate probiotic compounds to produce synergetic effect.^{20,23}

A recently published meta-analysis examined all published RCTs of synbiotics for the treatment of AD, using the SCORAD index to evaluate efficacy. The final analysis included 6 studies with 369 children. The authors concluded that the use of synbiotics for at least 8 weeks with mixed-strain bacterial species had a significant effect on improving the SCORAD index. This effect held only for children aged 1 year or older.²⁰ Theoretically, optimal synbiotic preparations are expected to obtain better results in AD prevention or treatment than probiotics or prebiotics alone.²³

CONCLUSION

Atopic dermatitis is a chronic residue skin disease, occurs mostly in children, but also can be occurs in adults. The correlation between probiotics and the immune system is thought to be through the ability of

probiotics to adhere to the surface of intestinal epithelial cells. The attachment of probiotics to the intestinal epithelial wall can inhibit the development of a Th2 mediated allergic response. Giving probiotics recommended for AD, which is 10⁹ for a period of 2 to 8 weeks, is said to be able to reduce the SCORAD index. Prebiotics have the potential to create a nutrient-rich environment in the gut in which microflora can thrive. Changes in the microflora can provide an allergic protective effect by modulating postnatal immune development. Synbiotic is a combination of prebiotics and probiotics, that have a synergetic effect. Optimal synbiotic preparations can be expected to obtain better results in AD prevention or treatment than either pro- or prebiotics alone.

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