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LITERATURE REVIEW

The role of dietary fiber or prebiotics in atopic dermatitis

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Abstract

Background: Atopic Dermatitis (AD) is a chronic inflammatory skin condition with itchy eczematous lesions, mostly found in children, and may affect a patient's quality of life. Individuals with AD were found to have dysbiosis of gut microbial, which may alter the immunologic tolerance of mucosa, causing inflammation and affecting skin conditions. Dietary fiber or prebiotics consumption may have a role in reversing dysbiosis and may have an effect on AD. In this literature review, the authors would like to further explore the role of dietary fiber or prebiotics in the prevention and alternative treatment for AD.

Methods: This study is a narrative literature review. The literature search was conducted in several sources: Pubmed, EBSCOHOST, Proquest, and Google Scholar, using keywords: "atopic dermatitis, atopic eczema, dietary fiber, prebiotic, nutrition". Our inclusion criteria were : 1) Studies in Randomized Clinical Trial (RCT), case report, case series, literarture review, systematic review, meta-analysis, cohort, and experimental studies, 2) available in full text, 3) written in English. Our exclusion criteria were : 1) Studies conducted more than 10 years ago (before 2012) and 2) lack of available data.

Discussion: Dietary fiber, particularly soluble fibers and those which can be fermented by gut bacteria (including prebiotics), plays a role in maintaining homeostasis of normal gut flora by producing SCFA, which increases the gut barrier, has anti-inflammatory properties, balances Th1/Th2 ratio, increases lymphocytes in *gut-associated lymphoid tissues* (GALT) system, and increases secretion of intestinal IgA. The role of dietary fiber/prebiotics in the prevention or decreasing rate of AD is still a matter of debate. Several studies showed no effect or correlation of prebiotic supplementation in decreasing the AD rate in pregnant women or babies with a high risk of atopy. On the other hand, several studies on prebiotic supplementation for babies and children have shown the benefits of prebiotic supplementation in preventing allergies (AD, rhinoconjunctivitis, and urticaria).

Conclusion: The role of dietary fiber or prebiotics in preventing or treating AD is still a matter of debate. Different study results make it difficult to conclude the clinical effect of prebiotics in allergy prevention, particularly AD. This may be caused by the heterogeneous studies and the limited number of studies on humans. Further studies (RCT) involving large-scale respondents are needed to define the effects of prebiotic supplementation in the prevention or alternative therapy for AD.

Keywords: atopic dermatitis, atopic eczema, children atopic dermatitis, dietary fiber, dysbiosis, elderly atopic dermatitis, prebiotic, nutrition

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin condition with a global prevalence of 20% in children and 5% in adults, presenting as dry, itchy skin and eczematous lesions with erosion, oozing,

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crusts with varying degrees of severity and may have an impact on quality of life.[1,2] The pathophysiology of AD has not been fully elucidated, although it was believed that the combination of the dysfunctional epidermal barrier, immune dysregulation, and environmental factors contribute to AD.[3] Furthermore, gut microbial are known to play a role in gut tissue and skin homeostasis. Dysbiosis on gut microbial diversity will alter mucosal immune tolerance and create an inflammatory microenvironment that will affect the skin condition. Several skin conditions, including acne vulgaris, psoriasis, rosacea, and AD, are associated with intestinal dysbiosis, manifesting in the skin through the gut-skin axis.[4,5] Decreased levels of microbiome such as *Lactobacillus and Bifidobacterium* and increased bacteria proportion of *E. coli, C.difficile*, and *S.aureus* are found in atopic patient's digestive systems. This condition could decrease the production of regulatory T cells and play important role in the pathogenesis of AD.[2,5]

The chronic natural history of AD and the need for long-term therapy with several adverse events potentials make patients, and their parents look for alternative therapies such as dietary modification.[3] Dietary fiber is defined as a carbohydrate group sourced from plant-derived food that cannot be completely broken down by human digestive enzymes and metabolized by microbes in the colon. Fiber consumption may increase the production of short chain fatty acid (SCFA), which increases the epithelial barrier function of the gut, improves immune system recruitment, and regulates inflammatory response.[4,6] In this literature review, the authors would like to dig deep into the role of fiber as the preventive or alternative therapy for atopic dermatitis.

Methods

This study is a narrative or traditional literature review. The literature search was conducted in several sources: Pubmed, EBSCOHOST, Proquest, and Google Scholar, using keywords: "atopic dermatitis, atopic eczema, dietary fiber, prebiotic, nutrition". Our inclusion criteria were : 1) Studies in randomized clinical trial (RCT), case report, case series, literarture review, systematic review, meta-analysis, cohort, and experimental studies, 2) available in full text, 3) written in English. Our exclusion criteria were : 1) Studies conducted more than 10 years ago (before 2012) and 2) lack of available data.

Discussion

Atopic Dermatitis

Atopic Dermatitis (AD), or commonly known as eczema, is a chronic inflammatory skin condition with increasing incidence in recent decades, particularly in developing countries.[7] According to the World Health Organization (WHO), AD affects 230 million people globally.[8] Atopic dermatitis is commonly found in children, with an estimated prevalence of 15-25%, and a varied prevalence of 1-10% in the adult population.[9] Atopic dermatitis is also commonly found in people with other atopic diseases called "atopic march," including allergic rhinitis, asthma, and food allergy.[10]

Atopic dermatitis is a multifactorial disease involving the interaction between genetic factors, immunity, and environmental factors. The strongest risk factor for AD is a family history of atopic disease, particularly AD. Other factors include living in urban areas, areas with low UV exposure, dry climate, diets with high consumption of sugar and polyunsaturated fatty acids, repeated consumption of antibiotics prior to 5 years of age, and higher socioeconomic status.[11] Pathogenesis of AD includes complex sequences involving skin barrier dysfunction, dysregulation of the systemic and cutaneous immune system, dysbiosis of the skin microbiome, and genetic factors.[12] Barrier dysfunction leads to chronic inflammation with epidermal hyperplasia and cellular infiltrates, including dendritic cells, eosinophils, and T cells. In the acute phase, there is a predominance of Th2-secreting IL-4, IL-5, IL-13, IL-25, and IL-31. Meanwhile, during the chronic phase, dominance switching occurs from Th2 to Th1.[7]

Microbiota diversity is known to decrease in individuals with AD's skin. Cutaneous colonization of Staphylococcus aureus occurs in 90% of AD patients, and the expression of virulence factors

have been proven to have a role in the pathogenesis of superficial or invasive infection, which contributes to AD exacerbation through the immune cell and keratinocyte regulation.[12] Aside from the skin, disturbance to gut microbiomes affects immune system homeostasis through metabolite production, which may create an inflammatory microenvironment. Combinations of these factors contribute to the development, persistence, and severity of AD through immunologic, metabolic, and neuroendocrine pathways, although few studies have shown conflicting results.[13]

Atopic dermatitis manifestation is characterized by acute eczematous flare-ups, oozing in the dry skin with an itching sensation. Chronic lesions may present as erythematous plaque to dried hyperpigmentation with lichenification or fissures. An itching sensation at night may cause sleep disturbances and fatigue and affect one's mental health.[14] To date, there is still no pathognomonic diagnostic test or laboratory biomarker to diagnose AD, so diagnosis is established based on history taking and physical examination. Several criteria have been used in diagnosing AD, with Hanifin and Rajka.[9] criteria being the most commonly used in the world.

Numerous scorings used to assess the severity of AD includes Eczema Area and Severity Index (EASI); SCORing Atopic Dermatitis (SCORAD); Physician Global Assessment (PGA). SCORAD >25 is considered mild AD, and SCORAD >50 is considered severe AD. Severe AD is associated with sleep disturbances, and in children, this leads to growth disturbances, low performance at school, attention disorder, and hyperactivity.[7,9] The treatment goal of AD is to alleviate the itching sensation and control this chronic disease in the long term so that the patient may function optimally at home, the workplace, and school. Listed below are the recommended therapy for AD patients based on European guidelines for the treatment of atopic eczema.[9]

Definition, Classification, and the Role of Dietary Fiber/Prebiotics

Dietary fiber definition has been a constantly evolving matter of debate.[15] Several countries define dietary fibers according to the Codex Alimentarius Commission definition in 2009, which definesdietary fibers as carbohydrate polymers with three or more monomeric units which are resistant to digestive enzymes (therefore, it does not get hydrolyzed and absorbed in the small intestine of humans) and meet the following criteria: (1) carbohydrate polymers naturally occurring from food such as fruits, vegetables, legumes, and cereals; (2) carbohydrate polymers obtained from food raw material which have physical, enzymatic or chemical effects on health; and (3) synthetic carbohydrate polymers proved scientifically to have physiological benefit.[15] The European Food Safety Authority (EFSA) defines dietary fiber as non-digestible carbohydrates plus lignin which includes non-starch polysaccharides (NSP) (cellulose, hemicelluloses, pectins, hydrocolloids (e.g. gums, mucilages, β-glucans)), resistant oligosaccharides, resistant starch, and lignin associated with the dietary fiber polysaccharides.[15]

Prebiotics is frequently associated with dietary fibers, but not all dietary fiber is prebiotics.[16] Currently, prebiotics is defined as undigested substance by digestive enzymes and acts as substrate for the growth and/or activity of one or more healthy bacteria species in the colon, particularly the growth of *bifidobacteria* and *lactobacilli* species.[16,17] Examples of prebiotics which are fibers that may be fermented and being studied to enhance the immune system are inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and xylooligosaccharides (XOS).[16]

Dietary fiber is classified based on the food source, chemical structures, solubility in water, viscosity, and fermentability.[16,18] Chemically, dietary fiber is classified as resistant oligosaccharides (Ros), including fructooligosaccharides (FOS) and galactooligosaccharides (GOS), resistant starch (RS), and non-starch polysaccharides (NSPs).[18]

Table 1 Treatment recommendation for AD patients.[9]

Atopic dermatitis severity	Treatment recommendations	
	Children	Adults
Baseline : basic therapy	Educational programs, emollients, bath oils, and avoidance of clinically relevant allergens	
Mild : SCORAD <25 or transient eczema	Reactive therapy with topical glucocorticoids class II or depending on local cofactors (topical calcineurin inhibitors, antiseptics inducing silver, silver coated textiles	Reactive therapy with topical glucocorticoids class II or depending on local cofactors (topical calcineurin inhibitors, antiseptics inducing silver, silver coated textiles
Moderate : SCORAD 25-50 or reccurent eczema	Proactive therapy with topical tacrolimus or glucocorticosteroids class II or III, wet wrap therapy, UV therapy (UVB 311 nm), psychosomatic counselling, climate therapy	Proactive therapy with topical tacrolimus or glucocorticosteroids class III, wet wrap therapy, UV therapy (UVB 311 nm, medium dose UV A1), psychosomatic counselling, climate therapy
Severe : SCORAD >50 or persistent eczema	Hospitalization, systemic immunosuppression : cyclosporine A, methotrexate, azathioprine, mycophenolate mofetil	Hospitalization, systemic immunosuppression : cyclosporine A, short course or oral glucocorticosteroids, dupilumab, methotrexate, azathioprine, mycophenolate mofetil, PUVA, alitretinoin

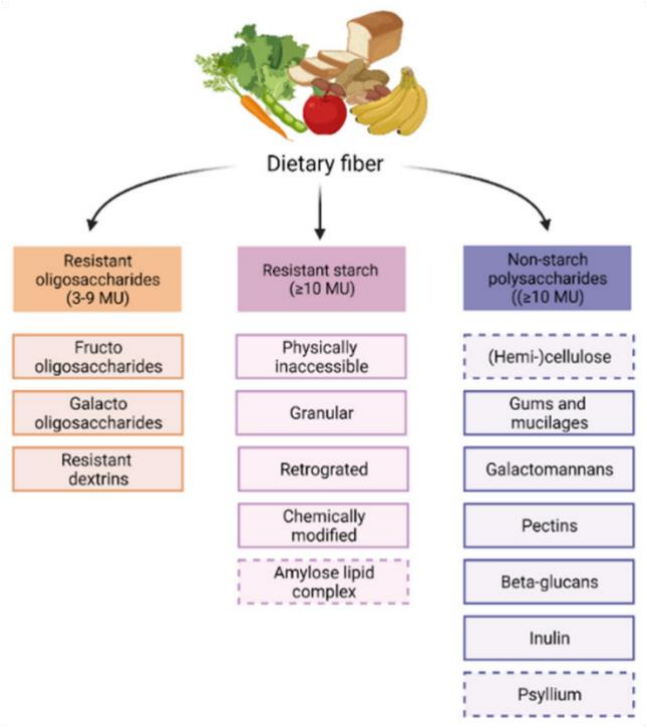

Figure 1 Classification of dietary fiber based on chemical structure. There are three groups of dietary fiber based on chemical structure: resistant oligosaccharides, resistant starch, and non-starch polysaccharides. The dotted square represents unfermented fiber.[18]

Soluble and insoluble fiber are commonly found in food sources such as legumes, vegetables, beans, seeds, fruits, and cereals. Meanwhile, RS can only be found in flour-containing foods such as cereals, legumes, tubers, and unripe fruits such as green bananas.[15,18] Insoluble fibers such as cellulose and hemicellulose are not fermented by gut bacteria but play a role in increasing transit time in the gut, solidifying the feces, and increasing the clearance process by defecation.[16,18] Soluble and fermented by gut bacteria fibers including Ros, all of RS (except amylose-lipid complex), and NSP (except hemi-cellulose and psyllium) have a role in immune system modulation. Dietary fiber containing non-digestible carbohydrates comes from polysaccharides plants, plants, or human milk-derived oligosaccharides.[16,18] These dietary fibers are resistant to the enzymatic and chemical digestive process, thus, cannot be digested or absorbed, reaching the colon and fermented by gut bacteria to become short-chain fatty acid, SCFAs: acetate, propionate, and butyrate, which has local and systemic anti-inflammatory properties.[15,17,18] Short-chain fatty acid (SCFA) and other metabolite products from fermentation by gut microbiota affect the immune system through several mechanisms: (1) enhancing intestinal barrier; (2) anti-inflammatory effect through activation of free fatty acid receptors such as G-protein-coupled receptor (GPR) 43, GPR41, and GPR109A which modulate homeostasis of the gut and regulate immune response; (3) inhibition of histone deacetylases which regulates rapamycin (mTOR)-S6K pathway for differentiation of T cell to effector and regulatory T cell and balance the ratio of Th1/Th2; (4) increasing the number of lymphocytes and/or leukocytes in gut-associated lymphoid tissues (GALT) and (5) increasing the secretion of intestinal IgA.[18–21]

Effect of Dietary Fiber/Prebiotics on Atopic Dermatitis

Diet influences dermatitis atopic.[15] Westernized diet commonly adopted in the modern world is dominated by processed food containing high calories, fat, and low fiber.[22] In a low-fiber diet, bacteria will break down the glycoprotein layer in the mucous layer of the gut as alternative energy, compromising the gut barrier.[5,22] A diet containing soluble fiber can be fermented by gut bacteria (prebiotics) and enhance the development of the gut microbiome in humans.[5,23] The gut microbiome plays a role in the maturation of Th1 cell and T cell regulator function and attenuates Th2 cell response, particularly in the fetal period.[2,16,17] Disruption in the homeostasis of normal gut flora (dysbiosis), particularly in the neonatal period, may result in an atopic cofactor, including atopic dermatitis.[24,25] Atopic dermatitis patients have increased gut bacteria such as *Escherichia coli*, *Clostridium difficile*, and *Staphylococcus aureus*; and decreased good bacteria such as *Lactobacillus* and *Bifidobacterium*.[17,25,26] The decreasing number of SCFAs-producing bacteria results in an imbalance production of T cell regulators, leading to an

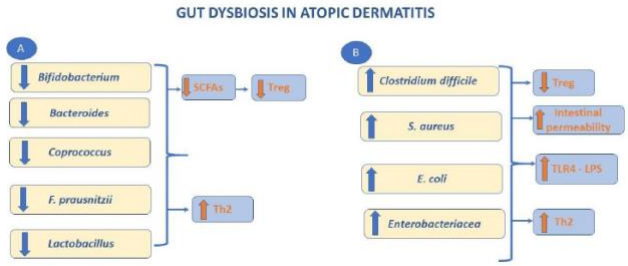

Figure 2 Gut dysbiosis in atopic dermatitis. (A) Decreased levels of microbiome such as *Lactobacillus and Bifidobacterium* and increased bacteria proportion of *E. coli, C.difficile*, and *S.aureus* in the digestive system in atopic patients. (B) *Bifidobacterium* and *Lactobacillus* metabolites have the ability to decrease cytokines associated with Th2 cells. Decreasing numbers of SCFA-producing bacteria cause decreased production of regulatory T cells.[25]

imbalance in the immune response of Th1/Th2, which results in increased Th2 cell and pro-inflammatory cytokines derived from Th2 cells.[17,25]

Modification of diet containing fibers/prebiotics may emend gut dysbiosis.[2,17] Prebiotics increase the production of SCFAs (acetate, propionate, and butyrate), which have anti-inflammatory properties, inhibition of pro-inflammatory cytokines from Th2 cells such as IL-4, IL-5, IL-6, IL-13, and decrease the level of IFN-γ (pro-inflammatory cytokines from Th1 cells), balancing out ratio of Th1/Th2, and increasing GALT system and intestinal IgA secretion.[2,17,19]

Dietary Fiber/Prebiotics Supplementation in Pregnancy and Lactation

There are still limited studies on prebiotic supplementation in pregnant and lactating women. Two preclinical studies conducted by Hogenkamp et al.[26] and another study by Fujiwara et al.[24] explored the effect of prebiotics supplementation during pregnancy on pulmonary resistance and atopic dermatitis-like skin lesion using model allergic mice. These three studies showed that there are decreased allergic responses in the model mouse given prebiotics, compared with the control group.[25] A recent study by Laigaard et al.[27] explored the effects of a prebiotic, xylooligosaccharide (XOS), on the gut microbiota and ear inflammation in an oxazolone-induced dermatitis model in BALB/c mice. This study reported that prebiotic supplementation in mice models resulted in increased levels of *Prevotella* bacteria in the gut and decreased serum IgE and pro-inflammatory cytokines in ear tissue biopsy.[27] These animal model studies showed the potential of prebiotic supplementation in pregnant and lactating women to decrease AD risk.

The first observational cohort conducted by Pretorius et al.[21] of 639 mother-infant pairs (all infants had a family history of allergic disease) investigated maternal intakes of total fiber, soluble fiber, insoluble fiber, resistant starch, and prebiotic fiber by a semi-quantitative food frequency questionnaire at 36–40 weeks of gestation. Infants then underwent clinical allergy assessment at 12 months of age through history taking, physical examination, and skin prick testing for common allergens.[21] This study showed that higher maternal dietary intakes of resistant starch were associated with reduced doctor-diagnosed infant wheeze, adjusted odds ratio (aOR) 0.68 (95% CI 0.49, 0.95, $p = 0.02$). However, in contrast, there were increased numbers of doctor-diagnosed eczema aOR 1.19 (95% CI 1.01, 1.41, $p = 0.04$) and parent-reported eczema aOR 1.27 (95% CI 1.09, 1.49, $p < 0.01$) in mothers who consume high dietary intakes of resistant starch.[21] However, this study has several limitations: this study did not divide maternal resistant starch dietary intakes into the four sub-types of resistant starch (RS1, RS2, RS3, RS4), which have different structural compositions and functional properties. Moreover, this study did not collect the infants' nor the mother's stool samples, did not collect detailed infant feeding data (especially exclusivity of breastfeeding and accurate infant formula use) between birth and 12 months of age, whereas breast milk is an important prebiotic in infants' gut microbiota.[21] In this study, the authors did not find an association between prebiotic consumption during pregnancy in reducing allergic events in infants. However, in this study, the average prebiotic consumption was only approximately 1.4 grams/day, which was lower than the recommended amount in the Mediterranean diet of 3-11 g/day, and was more similar to the recommended amount in the Western-style diet in the USA of 1-4 g/day.[21] Low

fiber intake, such as a Western diet, may cause changes in the gut microbiome and decreased levels of SCFAs, which have anti-inflammatory properties that maintain gut barrier function.[22]

The World Allergy Organization (WAO) does not recommend prebiotic supplementation during gestation and lactation as a preventive measure for atopic dermatitis due to its lack of valid scientific evidence.[17] Further studies, particularly in clinical trial settings, are needed to explore dietary fiber subtypes' effect on pregnant women's microbiomes, AD prevention, an association between metabolome (mother and infant) and the development of the infant immune system.

Dietary Fiber/Prebiotics Supplementation in Infants and Children

Prebiotics are naturally sourced from breast milk which contains minimal 200 Human Milk Oligosaccharides (HMO), which was not found in cow milk. Therefore, exclusive-breastfed infants have more abundant *Bifidobacteria* gut bacteria, particularly *B.Bifidum*, *B.longus*, and *B.Breve* compared with formulated milk.[4,24,25] Exclusive-breastfed infants have decreased risk of AD compared with infants not receiving exclusive breastfeeding. Infants not receiving exclusive breastfeeding are commonly fed with formulated milk. Therefore, prebiotic supplementation in formulated milk is developed and marketed to resemble the benefit of HMO.[24] A combination of *galactooligosaccharides* (GOS) and fructooligosaccharides (FOS) (scGOS 90% and LcFOS 10%) is the frequently studied prebiotic supplementation. Acidic oligosaccharides (AOS), Polydextrose (PDX) (with or without lactulose), oligofructose, and inulin are also studied in several studies.[24]

A review study conducted by Sestito et al.[24] (12 double-blind randomized controlled trial studies) compared the effect of prebiotic supplementation (particularly a combination of scGOS,lcFOS, PDX, pAOS) in standard formula or hydrolyzed/amino acid-based formula on AD. Included studies showed that prebiotic supplementation is still controversial in the prevention of allergy due to the heterogeneous studies and different types of prebiotics.[24] Several studies in that review: a cohort by Moro et al.[24,28] of 259 infants with a high risk of atopy found that a hydrolyzed protein cow's milk-based formula supplemented with 90% scGOS−10% lcFOS, (8g/L) given starting at 2 weeks at the age to 6 months of age significantly reduced AD at the age of 6 months compared to the placebo group (8g/L maltodextrin) [intervention group: 9.8 vs. 23.1% placebo group ($P < 0.05$)] and increased the number of fecal *bifidobacteria*. A long-term study with a follow-up duration of 2 and 5 years conducted by Aeslanoglu et al.[24,29] has shown the benefit of prebiotic supplementation as allergic prevention (i.e., atopic dermatitis, rhinoconjunctivitis, and allergic urticaria). Another RCT study found a 44% decreased incidence of AD at 1 year of life in infants at low risk of allergy fed with formula supplemented with GOS/FOS and specific pectin-derived acidic oligosaccharide compared to infants fed standard formula.[24]

Supplementation with prebiotics also showed a beneficial effect in children aged 1–4 years old.[30] In a double-blind, randomized, controlled trial, 125 children who were given cow's milk containing DHA, the prebiotics polydextrose (PDX) and galactooligosaccharides (GOS), beta-glucan, zinc, iron, vitamins A and D, were compared to 131 children fed with standard cow's milk for 28 weeks. Children who consumed milk enriched with prebiotics had significantly reduced episodes of allergic manifestation, including eczema and urticaria, allergic rhinitis and conjunctivitis, and wheezing when compared to the control group.[24,30]

Not all studies showed a beneficial effect of prebiotic supplementation on AD prevention.[24] Several studies showed that prebiotic supplementation did not have any benefit or effect on preventing or reducing AD incidence. A systematic review by Cueloo-Garcia et al.[31] reported that there was no strong evidence of prebiotic supplementation to prevent allergic risk, including AD.[1] A 2016 study conducted by WAO using Grading of Recommendations Assessment, Development, and Evaluation (GRADE) about prebiotic supplementation in non-exclusively breastfed infants found that there were no differences in numbers of eczema (RR; 0,57, 95% CI:0,30-1,08) in five meta-analysis studies

involving 1.313 infants.[32] Another study by Ranucci et al.[33] showed that formula supplemented with galactooligosaccharides/polydextrose (GOS/PDX) did not significantly decrease the cumulative incidence of AD in the first year of life, compared with standard formula and exclusive breastfeeding. Until now, from the study we have collected, there are no studies that make a benchmark for doses or types of fiber used for the prevention of atopic dermatitis because the study of fiber as prevention of atopic dermatitis still has various results (some provide benefits in the declining prevalence of atopic dermatitis, but some are not). It could be caused by the heterogenous studies, methods, and sampling.

Dietary Fiber/Prebiotics Supplementation in Adults

There are not many studies that discuss the role of giving fiber in the prevention of atopic dermatitis in adults. One of the studies conducted by Lee et al.[6] who examined the relationship between dietary fiber intake and allergic diseases (asthma, allergic rhinitis, and atopic dermatitis) carried out on 10,479 adults, which is divided into 4 quartiles (Q1-Q4) based on the amount of fiber consumption using data from the Korean National Health and Nutrition Examination Survey (2010-2011), reporting that there was a decrease in the prevalence of asthma (Q4 OR: 0,656; 95% confidence interval (CI): 0,48-0,91, *p* for trend < 0,0001) and atopic dermatitis (Q3 crude OR: 0,746; 95% CI: 0,57-0,98; Q4 adjusted OR: 0,712; 95% CIL 0,50-1,01, *p* for trend < 0,0001) in groups that consumed higher dietary fiber.[6] The disadvantage of this study is that this study does not evaluate further the improvement of atopic dermatitis symptoms in patients who consume higher fiber, the results only find a decrease in the prevalence of atopic dermatitis patients in groups who consume higher fiber.[6] From the study we examined, no one explained the amount, dose, and type of fiber that adults must consume to prevent atopic dermatitis. This is because there is still a lack of research on the evaluation of dietary fiber intake and atopic dermatitis in adults. After all, research on fiber intake is more centered in the prenatal period and during the period of infants and children, where the incidence of atopic dermatitis is more in that period than in adults.

Conclusion

Supplementation of prebiotics/dietary fibers in the prevention and management of atopic dermatitis is still a matter of debate. Due to the heterogeneous studies and the limited number of studies done in humans, different study results make it difficult to conclude the clinical effects of prebiotics in allergy prevention, particularly atopic dermatitis. Therefore, further studies, particularly large-scale randomized controlled trials and meta-analyses on pregnant women, atopic infants, and infants with high risk of atopy, are needed to better understand the benefit of prebiotic supplementation in the prevention and non-pharmacological therapy of atopic dermatitis.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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