

**IN THE NAME OF
GOD**



The role of Prebiotics And Probiotics In Atopic Dermatitis



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Atopic Dermatitis (AD)

- **Chronic** disease
- Inflammatory and dry skin
- Intense **pruritus**
- Eczematous cutaneous lesions
- Intense pruritic papules towards lichenification
- May associate **allergic rhinitis , Asthma**
- Prevalence is increasing (10-20% in pediatric))
- Up to 3% of adults
- Onset occurs during the first year of life



- Complex etiopathogeny



Multifactorial :

- Genetic factors
- Environmental factors and
- Immunological factors



Increasing risk of allergic diseases and AD :

- The composition of intestinal and cutaneous microbiome
- Maternal diet during pregnancy
- Mode of delivery
- Antibiotic treatment during pregnancy and early infancy
- Westernized lifestyle (chronic exposure to allergens)



- Severity of AD assessed using the **SCORAD**
(Severity Scoring of Atopic Dermatitis)





Prebiotics AND Probiotics



Prebiotics

- Non-digestible ingredients
- Beneficially affect the host by ;
- Selectively stimulating growth or
- limiting some species of intestinal bacteria (Bifidobacterium and Lactobacilli) improve the health of the host

Probiotics

- living microorganisms that confer a health benefit on the host when there are administered in adequate amounts

The most known microorganism used as probiotics

Lactobacillus family:

- Acidophilus, sporogenes, lactis, reuteri RC-14, GG, L. plantarum 299v

Bifidobacterium:

- bifidum, longum, infantis,

Streptococcus group:

- thermophilus, lactis, fecalis

Non-bacterial organisms

- Non-pathogenic yeast Saccharomyces boulardii

• Lactobacillus and Bifidobacteria :

- Normal microbial flora
- Gram-positive
- Anaerobic bacteria
- Several types produce lactic acid
- hydrogen peroxide
- bacteriocins

Gut microbiome



- Numerous biological and metabolic functions
- Alteration of the intestinal bacteria balance :
- **Inflammation** (LPS)
- Binding to the CD14/Toll-like receptor 4 (TLR-4) complex
- Influence the **metabolism of the host** by :
- modulating the tissue composition of fatty acids
- Lactobacilli and Bifidobacteria produce bioactive isomers of conjugated linoleic acid with immunomodulating properties, **reducing the proinflammatory cytokines**
- Synthesizes of **glycosidic hydrolases**
- **Monosaccharides**
- Short chain fatty acids (**SCFAs**) (acetate, propionate, butyrate)

Short chain fatty acids (SCFAs)



- Important role in energy **metabolism**;
- **Butyrate** (energy for colonic epithelial cells, IBD, intestinal disease)
- **Propionate** (lipogenesis and hepatic gluconeogenesis)
- **Acetate** (substrate for cholesterol synthesis)

Role of Probiotics in colon:



- Modulate the intestinal microbiome and immune status
- Improving the **intestinal barrier**
- **Reducing allergic** phenomenon and AD severity
- Intestinal permeability increased in AD
- Babies (caesarean section) have a lower colonization with Bacteroides and higher with Clostridium
- Early colonization with **Escherichia coli** has a **protective** role for AD

Skin microbiome and AD



4 strains prevailing on the skin surface:

- 1-Firmicutes (Staphylococcus, Streptococcus, Anaerococcus, Finegoldia, Veillonella, Lactobacillus, Peptoniphilus),
 - 2-Actinobacteria (Propionibacterium, Corynebacterium, Micrococcus, Kocuria, Actinomyces, Rothia),
 - 3-Proteobacteria (Acinetobacter, Haemophilus, Enhydrobacter, Neisseria, Microvirgula), and
 - 4-Bacteroidetes (Prevotella, Chryseobacterium, Fusobacteria, Leptotrichia)
- Most common genus is Staphylococcus
 - Most common species in healthy skin is Staphylococcus epidermidis

Cutaneous microbiome in AD



- Reduction of the **cutaneous microbiome** diversity in **AD**
- Early colonization with **Staphylococcus aureus**
- Cutaneous *Staphylococcus epidermidis* protective effect against AD
- Association between AD severity and **Corynebacterium**
- **Severity and chronicity** of **eczema** appear to be more important determinants of **skin microbiome** configuration



- Increase in **fungal diversity** : Malassezia restricta, globosa and dermatitis in **~90%** of AD
- AD have **IgE mediated** sensitization to **Malassezia** species (positive skin prick tests)
- Correlates with **disease severity**
- **Demodex mites** (Demodex folliculorum and Demodex brevis) was not associated with an increased prevalence of AD

Modulating the human microbiome by pre- and probiotics

- **Gut microbiome** genetic material of all microbes:
- Bacteria , Fungi ,Protozoa and Viruses living inside digestive tract of humans and animals
- Composition of human microbiome varies depending on:
 - Age
 - Sex
 - Antibiotics
- **Bacteria** dominant microorganisms in the colon > 1,014 belonging to ~500-1,000 distinct species
- **Human intestinal microbiome is related to the host**
- **No two human beings with identical intestinal microbiome**

Prebiotic and Probiotic in AD



- In the past few years, more ongoing studies evaluated the administration of pre- and probiotics in patients with atopic dermatitis

Prebiotics and Probiotics in infants



- **Prebiotics administration :**

- In the first year of life reduce the risk of **asthma or food allergy**
- In **atopic dermatitis** were inconclusive

A systematic review of a meta-analysis (8 clinical trials, 741 infants)

- **Beneficial effect** of Lactobacillus-containing probiotics on **AD** severity
- Probiotics , Bifidobacterium (3 studies, 73 infants) did not prove beneficial effects
- small number of subjects and heterogeneity
- Most meta-analysis followed patients < 8 weeks
- Previously published: smaller number of Bifidobacteria strains in the children's feces with AD
- Conclusion:

Infants with moderate and severe AD presented a protective effect of probiotics

Prebiotics and Probiotics in children (1-18 years)

- Meta-analysis (568 children, 1-18 years) improvement in **SCORAD** of children AD given **probiotics**
- **Lactobacillus** and a **mixture** of different strains (Bifidobacterium bifidum, Lactobacillus acidophilus, Lactobacillus casei and Lactobacillus salivarius)
- Recent randomized, double-blind, placebo-controlled intervention trial (50 children 4-17 years, mixture of probiotics between 4-12 weeks) reducing SCORAD

Type of probiotics used in clinical trials



- Probiotic micro-organisms **must be appropriate** :
- **Non-pathogenic** and
- **Non-toxic** for human consumption
- **Toxicity tests**
- Must not affect **taste, texture**
- Must **survive** in the probiotic food in a sufficiently large concentration until they are consumed

Prebiotics - mechanism of action



- Enhance the production of **SCFAs** (acetate, propionate, butyrate) **anti-inflammatory** effects
- Reduce the generation of **toxic fermentation** products
- **Improve** the **Th1/Th2** ratio
- **Increased lymphocyte** and/or leucocyte numbers in gut-associated lymphoid tissues (GALT)
- Increased **intestinal IgA** secretion

Probiotics - mechanism of action



- Immunomodulatory effect
- Reduce the severity of AD
- Inhibiting T-helper 2 mediated response
- Improving the Th1/Th2 ratio
- Inhibiting cytokines IL-4, IL-5, IL-6 ,IL-13
- INF- γ decrease (cytokine released by Th1 cells)
- Phagocytosis
- Serum IgA is increased
- Stimulate the secretion of IL-10 and transforming growth factor- β (TGF- β)
- Reduce inflammation by reducing proinflammatory (cytokines IL-4, IL-6, TNF- α , INF- γ , hsCRP)



- Increasing expression :
- **IL-10**
- T Reg-related cytokines at mesenteric lymph nodes
- Inhibition of mature **dendritic cell differentiation**
- Inhibition transformation of **naive Tcells into Th2**
- Immunomodulation decreases the susceptibility to inflammatory and **allergic factors**
- Modulating the **intestine-skin axis**
- Modulate **intestine-brain axis**



- **In newborns**, the **distribution** of different **Bifidobacterium** species in the faeces influences the prevalence of allergic diseases
- In a study : **different** Bifidobacterium species in faeces of children with allergies compared to **healthy** ones,
- Significantly higher levels of **Bifidobacterium longum** in **healthy** children
- This strain **prevents** the occurrence of bronchial **asthma** and **allergic dermatitis**

Medical nutrition therapy



- Important role in modulation of the intestinal microflora
- **‘functional food’ :**
- Prebiotics
- Probiotics
- Natural antioxidant
- Good metabolic effects
- Improving digestion and absorption of food , minerals, vitamin synthesis
- Improving overall nutritional status and **health**

Probiotic consumption



- Reduction of **blood glucose**
- Reduction of **insulinemia** and insulin resistance (**IR**)
- **Antioxidant** effects
- A recent meta-analysis :
Decrease of Alanine aminotransferase and IR in
non-alcoholic **fatty liver disease**
- **Decrease** in total cholesterol, TG , LDL
- **Increase** in HDL

Obesity And AD



- Systematic review and meta-analysis (Zhang and Silverberg)
- **Overweight and obesity** had a higher risk of **AD**
(in North America and Asia but not Europe)

Major limitations of this cross-sectional design

- A study in Germany

No increase of **AD** in patients with :

- Obesity
- Diabetes
- Hypertension and hyperlipidemia

Obesity, dyslipidemia and AD



- Mediated by **chronic systemic inflammation**
- Proinflammatory cytokines (IL-6, TNF- α and CRP)
- Increased oxidative stress and consequent change in expression of inflammatory genes

Conclusion



- Improving nutritional status
- High nutrient digestion
- Specific and non-specific immune response
- Beneficial effects on the GI and skin

**Supporting the use of pre- and probiotics
in patients with Atopic dermatitis**



- No enough data in the literature to respond to questions regarding :
- Optimal dosing
- Optimal time to start treatment
- Duration
- Personalized use of probiotics
- Most randomized controlled trials and meta-analyzes
- Probiotics for at least 8 weeks
- Beneficial effects in improving SCORAD of AD

