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:

- thermophillus, 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-Bacteriodetes (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 dermatis 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 heterogenity
- 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