IN THE NAME OF GOD

The role of Prebiotics And Probiotics In Allergy

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- The prevalence of allergic diseases such as :
- Asthma

- Allergic rhinitis
- Atopic dermatitis increased sharply over the past two to three decades in many

countries

- Allergies are now the most common chronic disease among children throughout the world
- Prevalence of Allergic rhinitis increased followed by an increase in
- Asthma prevalence and then Food Allergies
- Increasing in developing world related to a westernizing lifestyle, while decreasing in the industrialized world

Allergy risk factors

- Environmental changes , driving the allergy epidemic , not fully identified
- Hygiene hypothesis a strong case
- Reduction in general microbial exposure during early childhood
- Corresponding changes in commensal microbial
- Early exposure to pathogenic or nonpathogenic microbial products can either prevent or modify allergic responses
- Antibiotics , inappropriate foods disturb gut microbiota ,raise risk of allergy , especially in children

- 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)

- Microbial ecosystems cover the surface of the human body
- It is clear that our modern environment has profound effects on microbial composition and diversity
- Dysbiotic gut microbiota associated with allergic diseases , asthma in cross-sectional , observational studies
- One of the main incriminated factors , alteration of the postnatal immune maturation due to reduced microbial stimulations caused by modern life style
- Environmental factors and an aberrant gut microbiota with a shift of the Th1/Th2 balance towards a Th2 response

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

- Normal immune homeostasis is dependent upon gut microbiota
- Influenced by differences in colonization patterns
- The intestinal microbiota of pregnant mothers contributes greatly to the development of appropriate immune system and the health of the new born

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 proinflammatorycytokines
- 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)

- Declining microbial exposure , increase of allergic disease

- Gut microbiota confer specific immune-protective effects through complex pathways , gut-associated lymphoid tissue (GALT), largest immune" organ" in humans
- These effects include :
- Local immunoglobulin A (IgA) production
- Induction of tolerogenic dendritic cells
- Regulatory T cell populations (Treg)
- Production of cytokines, (IL) 10 and transforming growth factor (TGF) beta
- Inhibit local inflammation
- Improve gut barrier mechanisms
- Reduce inappropriate immune responses

Prebiotics AND **Probiotics**

Prebiotics

- Non-digestible carbohydrates ,fatty acids, phenolic ,phytochemical
- Accepted prebiotics :

Fermentable oligosaccharides inulin, Fructo oligosaccharides (FOS), Galacto oligosaccharides (GOS), lactulose

- Beneficially affect the host by ;
- Selectively stimulating growth or
- limiting some species of intestinal bacteria
- Improve the health of the host

Probiotics

- living microorganisms confer a health benefit on the host when administered in adequate amounts
- Commonly used probiotics :lactobacilli, bifidobacteria strains

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

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

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

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**

- Recently interest in the use of probiotics for the prevention and management of childhood allergic disease

- Selective probiotic strains have ability to increase microbial stimulation and hence modulate the immune response
- Clinical and randomized clinical trials have proven the efficacy of a limited number of probiotics
- Supplementation in pregnant women for the prevention of some allergic disorders in newborns

- Direct immune effect appears by the fermentation products of prebiotics
- Gut microorganisms ferment prebiotics produce shortchain fatty acids (SCFAs):

- Direct antiinflammatory effects
- Promote intestinal integrity through
- Epithelial cell proliferation , differentiation
- Affect both mucosal and systemic immunity
- **However, more studies are needed to confirm that these are clinically relevant effects**

Do probiotics affect allergies?

- Allergic children have a different intestinal flora from healthy children
- Higher levels of Clostridia and lower levels of Bifidobacteria

- Bifidobacteria and Lactobacilli are commonly in the intestinal flora of non-allergic children
- Human trials : limited benefit for the use of probiotics in atopic dermatitis
- Moderate benefit of probiotics for eczema prevention
- Whereas there is less evidence of a benefit for other allergic disease

- Use in allergic rhinitis are less robust
- Currently, no role for probiotic therapy in the treatment of bronchial asthma

- Probiotics in the prevention of wheezing and asthma in infants have no outcomes
- No significant efficacy for reducing nasal symptom in

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- Related to the multiple factors:
- Environment, strain selection, dosage, moment of administration, genetic background

- Therefore there is insufficient evidence to recommend the administration of probiotics in the prevention and management of :
- Allergic rhinitis
- Asthma
- Future studies will be critical in determining the exact role of probiotics in allergic disorders

- Physicians have a responsibility to ensure the efficacy and safety of any products they prescribe or recommend
- There is still insufficient evidence to recommend probiotics for the prevention of allergic diseases or as part of standard management for any allergic conditions in children

- The positive effect of probiotics related to:
- Type of probiotic strain
- Method of administration

- Onset time
- Dose size
- Duration of treatment
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- Patient and parent therapeutic education represent an important element of the treatment plan
- Future of AD treatment belongs to novel biological therapeutic agents coming in the recent years.

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

RECOMMENDATIONS FROM GUIDELINES

- Many experts bodies such as:
- The European Academy of Allergy and Clinical Immunology **(EAACI)**
- Food Allergy and Anaphylaxis Guidelines
- Not recommend using prebiotics, probiotics, or synbiotics for the prevention of any allergic condition
- because of great heterogeneity in the studies and variability in results • Others, such as :
- US National Institute of Allergy and Infectious Diseases **(NIAID)** have not given any recommendations

- World Allergy Organization **(WAO)** using prebiotics:
- Only in infants who are not exclusively breastfed
- Pregnant women
- lactating women when there is high risk of allergy in the children (presence of a biologic parent or sibling with asthma, allergic rhinitis, eczema, or food allergy)
- Prevention of eczema
- Not any other allergic disease
- Risk of adverse events was low

- Timing, duration, and choice of probiotic (strain and dose) are not specified in the WAO guidelines
- Given in the last 4-6 weeks of pregnancy
- Greater variability in timing and duration of postnatal therapy in the infant and/or breastfeeding mother
- Only probiotic strain with reproducible data is Lactobacillus rhamnosus GG (LGG)

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

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