Relationship between Dysbiosis and Allergic Diseases

Subjects: Pediatrics

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The intestinal microbiota is a diverse and complex microecosystem that lives and thrives within the human body. The microbiota stabilizes by the age of three. This microecosystem plays a crucial role in human health, particularly in the early years of life. Dysbiosis has been linked to the development of various allergic diseases with potential long-term implications.

allergy asthma atopic dermatitis children microbiome gut microbiota

1. Introduction

The gut microbiota represents the population of microorganisms that inhabit the human gut. Over the last decade, several studies have been conducted to determine the relationship between the microbiota and allergies in children. The findings suggest that the gut microbiota has a significant role in the promotion of these allergies. For instance, Penders et al. [1] conducted a comprehensive assessment of 18 studies investigating the connection between the microbiota of the gut and allergic diseases. These studies, published between 1999 and 2006, were mainly observational and compared the characteristics of the microbiota in allergic diseases. They analyzed the gut microbiota profiles of subjects with various allergic conditions, including atopic dermatitis, wheezing, food allergy, allergic rhinitis, and asthma. The methods used to evaluate the microbiota composition varied from traditional bacterial cultures to advanced molecular biology techniques. Most studies found a correlation between the composition of the microbiota and the presence of allergic clinical manifestations. However, it was difficult to differentiate between protective microorganisms and those linked to an increased risk of allergic diseases. Variations in study types and laboratory techniques used to evaluate the microbiota composition were attributed to differences in results [1].

Similarly, Melli et al. [2] conducted a study which analyzed research published between 2007 and 2013 and included 21 studies that examined the composition of the gut microbiota in allergic conditions. It was observed that compared to nonallergic children, those with allergies presented a lower level of biodiversity in their colonic microbiota, characterized by an overabundance of *Firmicutes* and a higher count of *Bacteroidaceae*. Another study conducted by Azad et al. in 2013 found that infants with a lower diversity of gut microbiota are at a higher risk of developing allergies later in life [3]. Other studies have stated that alterations in the composition of the microbiota have been linked to the onset of various diseases [4][5].

2. Development of the Gut Microbiota in Children

A study conducted by Odamaki et al. [6] in 2016 revealed that the gut microbiota undergoes age-related changes. Stool samples were analyzed from 367 healthy Japanese individuals ranging from 0 to 104 years of age using 16S rRNA sequencing. It was observed that the microbiota composition remained stable during adulthood, with *Firmicutes*, including *Lactobacillus* and *Clostridium*, being the most prevalent phylum in the intestinal microbiota among adult subjects. On the other hand, *Actinobacteria*, including *Bifidobacterium*, were more abundant in samples obtained from one-year-old participants, with their relative abundance decreasing after the weaning period. The intestinal microbiota developed to resemble an adult-like gut microbiota by the age of three.

Many studies have reported that the establishment of the human gut microbiota begins in fetal life through various sources; one of them is the detection of bacterial DNA in the placenta [7]. It is worth noting that there is ongoing debate among the scientific community regarding its presence in this organ (with some studies reporting the presence of bacterial DNA and/or live bacteria in the placenta, while others have failed to find conclusive evidence of a placental microbiome) [8][9]. These conflicting results have led to suggestions that any bacterial presence observed in the placenta could potentially be attributed to contamination during the collection or processing of samples. Furthermore, bacterial DNA has been found in the amniotic fluid [10] and meconium of children born by cesarean section, providing strong evidence for the colonization of the gut microbiota during early life [11]. After delivery of the fetus, it will come in contact with many different flora that will increase the population of the microecosystem. This has been observed in a study evaluating the bacterial quantity in the infant gut of subjects with vaginal delivery, who acquired abundant bacteria present in the vaginal and perianal area, which accelerates colonization of the intestinal microbiota as established through examining the gut microbiota of infants. A level of 107 bacteria per gram of stool on day 1 of life was reported, which increased to 109 per gram on day 3, 1010 per gram on day 7, and 1011 per gram by 6 months, almost reaching the level found in adults [12].

3. Factors Influencing Microbiome Development

The role of host genotype in shaping the composition of gut bacteria has only been acknowledged in recent times. To investigate the genetic factors involved, the traditional approach used is to compare data between monozygotic twins (MZ) and dizygotic (DZ) twins [13]. An extensive study conducted on twins (n = 416) reported that monozygotic twins have a more similar gut microbiota composition than dizygotic twins, highlighting the influence of genetic factors on the intestinal microbiome. Additionally, this study identified several heritable bacterial species, with the most heritable belonging to the family of twins [14]. Two years after the initial study, the same study group tripled the sample size with 1126 twin pairs. This larger cohort study validated previously discovered heritable bacteria and revealed novel associations between host genes and bacterial strains [15].

Another significant factor influencing microbiome development is the mode of delivery [16]. Infants born by vaginal delivery acquire bacterial species from the vaginal and perianal area such as *Lactobacillus*, *Prevotella*, or *Sneathia* spp. [17], while infants delivered via caesarean section have reduced exposure to these bacteria [18], resulting in a different composition of their microbiome [19].

Breastfeeding is also essential to shape the microbiome of infants. Breast milk contains various prebiotics, such as human milk oligosaccharides, which selectively promote the growth of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* [20]. However, infants who are fed with milk formulas have microbiomes such as *Roseburia*, *Clostridium*, and *Anaerostipes* [18]. Dietary factors also have another effect on the microbiome, such as high-fiber diet, which promotes the development of fiber-degrading bacteria, leading to a more diverse and stable microbiome [21]. Antibiotic use during infancy and early childhood has also been linked to alterations in the microbiome composition, potentially leading to dysbiosis [22]. Gestational age represents another determining factor; the preterm intestine is colonized mainly by *Enterobacter*, *Staphyloccoccus*, and *Enterococcus*, while in a full-term infant the colonization is mainly by *Bacteroides*, *Bifidobacterium*, *Parabacteroides*, and *Escherichia* [23]. Furthermore, environmental factors such as exposure to pets, urbanization, and sanitation can affect the microbiome, with increased exposure to microbial diversity generally associated with a more diverse composition [24].

The combination of these factors can disrupt the balance of the intestinal microbiota and cause dysbiosis, in some cases causing cardiac pathology such as heart failure and correlated with the severity of the disease [25][26]. Heart failure is associated with significant changes in the gut microbiome [27]. These changes include a reduction in core intestinal microbiota, decreased bacterial diversity, increased levels of potentially harmful bacteria, and a decline in the production of short-chain fatty acids [27]. Furthermore, some individuals with heart failure may present an increased intestinal permeability, allowing bacterial products to enter the bloodstream and contribute to disease progression. The microbiota plays an important role in immunity. Therefore, dysbiosis can create an environment that is more favorable for the growth and spread of harmful microorganisms such as *Shigella* spp. A retrospective study over a 10-year period, conducted on 376 patients with *Shigella* [28], revealed that children under five years old were more susceptible to *Shigella* spp. The study also found that atmospheric temperature, humidity, and rainfall were significant environmental factors influencing the incidence of *Shigella* spp. Similarly, in a retrospective study spanning a decade, from 1 January 2009 to 31 December 2018, researchers examined 377 patients diagnosed with *Salmonella* spp. disease [29]. The study findings indicate a significant correlation between the occurrence of *Salmonella* spp. cases and elevated humidity and atmospheric temperature levels. These environmental factors could have initiated dysbiosis which led to the child intestine vulnerability to *Salmonella* species. However, there is a limited amount of published research to support the hypothesis.

4. Microbiome, Obesity, and Body Health

The microbiome is involved in various aspects of body health in children. For example, analyses have illustrated that the microbiome is taking part in the development and maturation of the immune system in children [30][31][32]. The gut microbiome has been shown to play a critical role in immune system development, as it is involved in the production of immunoglobulins and other immune system components [33]. A study published by Blanton et al. [34], has shown that the configuration of the intestinal microbiota during childhood can have a significant impact on body growth and development, and that underweight children presented a less-diverse gut microbiota compared to healthy children. The researchers suggested that the less-diverse microbiota could lead to poor nutrient absorption,

resulting in stunted growth. The gut microbiota in individuals with obesity has been found to have a heightened ability to ferment polysaccharides from the diet, which are typically indigestible by the host. This results in increased absorption of monosaccharides and short-chain fatty acids (SCFA), promoting the liver conversion of complex lipids and subsequent deposition of adipocytes [35].

Research has revealed a correlation between dysbiosis, elevated levels of SCFA, obesity, and metabolic alterations. However, the precise connection between SCFAs and obesity remains uncertain [36][37]. SCFAs, which are produced by the intestinal microbiota, play a fundamental role in regulating intestinal permeability, bile acid metabolism, inflammation, and immune functions. In individuals with obesity, it is suggested that an increased production of colonic SCFAs allows for greater microbial energy harvest. However, certain SCFAs can also activate specific peptide hormones, stimulating feelings of satiety and promoting glucose disposal in peripheral tissues [37]. A study conducted by Ley et al. [38] reported that the gut microbiota of obese individuals was distinguished by a greater proportion of *Firmicutes* and a lesser proportion of *Bacteroidetes* compared to underweight subjects. Another study by Liu et al. [39] determined the association between dysbiosis and obesity. A more recent study investigated the effects of a high-fat diet on the gut microbiota of human subjects. The authors found that the high-fat diet resulted in alterations in the gut microbiota that were associated with increased obesity [40]. In conclusion, the intestinal microbiota maintains a vital part in the development of obesity. Dysbiosis and altered constituents of the intestinal microbiota in individuals with obesity promote the fermentation of indigestible dietary polysaccharides and the absorption of SCFAs, ultimately leading to an increased deposition of adipocytes. More research is needed to completely understand the complex connection between SCFAs, the gut microbiota, and obesity.

5. The Relationship between Dysbiosis and Allergic Diseases

Dysbiosis, defined as an imbalance or maladaptation in the microbiota, is increasingly recognized as a significant factor in the development of allergies in children [41]. The normal population of the intestinal microbiota aids in crucial physiological processes such as digestion [42], metabolism [43], and immune system regulation [44]. The complex interplay between gut microbiota dysbiosis and the development of allergic diseases has recently emerged as a topic of significant scientific interest [45][46][47]. In 2017, the first discovery was made by biologist Erik Wambre and immunologist William Kwok, who found that a specific type of cell, known as T helper type 2 cell, which produces Interleukin-4 (IL-4), Interleukin-5 (IL-5), Interleukin-9 (IL-9) and Interleukin-13 (IL-13), plays a critical role in triggering allergic reactions [48]. This was further demonstrated in February 2018 by multiple studies which determined a direct connection between T helper type 2 cells and allergen sensitization in allergic rhinitis [49]. Regardless of research spanning more than two decades on the use of immune molecules to prevent allergic diseases, no effective strategies have been established yet [50]. The composition of the gut microbiota is understood to be intrinsically linked to the maturation and regulation of the host's immune system, thus any perturbations in this delicate balance, such as those caused by dysbiosis, can potentially result in abnormal immune responses and, subsequently, allergic diseases [32][51]. The "hygiene hypothesis" puts forth that a diminished exposure to commensal and pathogenic microorganisms during early childhood may lead to a lack of adequate immune system stimulation and maturation [52]. In this context, dysbiosis may serve as a critical factor in

the increasing prevalence of allergies. Furthermore, certain bacterial species, including *Bifidobacteria* and *Lactobacilli*, play an essential role in sustaining immune homeostasis [53][54]. Their contribution to the stimulation of regulatory T-cells that can mitigate allergic responses, along with the promotion of anti-inflammatory cytokines such as IL-10, is significant [55]. Dysbiosis often results in a reduction of these crucial species, which can disrupt immune equilibrium and predispose individuals to allergic reactions. Additionally, a primary factor contributing to dysbiosis probably will be reduction in gut microbiota diversity, leading to decreased resistance to pathogenic microorganisms and immune system weakening [56]. This can potentially result in allergic disease development. Moreover, dysbiosis can lead to an increase in intestinal barrier dysregulation, allowing allergens to enter the bloodstream and trigger an immune response thought to occur due to the release of inflammatory mediators and cytokines (e.g., IFN-γ, TNF-α) that lead to degradation of the intestinal barrier [57][58]. Lastly, an interesting new hypothesis suggested that dysbiosis resulting from various factors including cesarean delivery and antibiotic use leads to a decrease in butyric-acid-producing bacteria (BAPB), which leads to a decrease in intestinal butyric acid concentrations [59]. The decrease in butyric acid concentration can suppress the differentiation of T-cells into regulatory T-cells (Tregs). The reduced number of Tregs impairs the immune system's ability to control excessive immune responses, thereby contributing to the onset of allergic diseases [59]. Some previous studies support this hypothesis, with one study showing that children with high levels of butyric acid in their stool samples at 18 months of age tend to have fewer sensitized allergens [60]. Following the hypothesis, prebiotics and probiotics can increase the levels of BAPB, and postbiotics that are rich in butyric acid could be a promising preventive or therapeutic approach to allergic diseases. Postbiotics are bioactive compounds released through the metabolic activity of microorganisms, and they can have beneficial effects on the host [61].

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