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Gut Microbiota, Probiotics, and Vitamin D: Interrelated Exposures Influencing Allergy, Asthma, and Obesity?

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Abstract

Current evidence supports a role for gut colonization in promoting and maintaining a balanced immune response in early life. An altered or less diverse gut microbiota composition has been associated with atopic diseases and/or obesity. Moreover, certain gut microbial strain or strains have been shown to inhibit or attenuate immune responses associated with chronic inflammation in experimental models. However, there has been no fully adequate longitudinal study of the relation between the neonatal gut microbiota and the development of allergic diseases (e.g., atopic asthma) and obesity. The emergence of promising experimental studies has led to several clinical trials of probiotics (live bacteria given orally that allow for intestinal colonization) in humans. Probiotic trials thus far have failed to show a consistent preventive or therapeutic effect on asthma or obesity. Previous trials of probiotics have been limited by small sample size, short duration of follow-up, or lack state-of-the art analyses of the gut microbiota. Finally, there is emerging evidence that the vitamin D pathway may be important in gut homeostasis and in the signaling between the microbiota and the host. Given the complexity of the gut micriobiota, additional research is needed before we can confidently establish whether its manipulation in early life can prevent or treat asthma and/or obesity.

Keywords

microbiota; asthma; obesity; allergic; eczema; vitamin D; probiotics; cytokines

Introduction

Asthma and obesity are two major public health problems in industrialized nations such as the United States.1–3 Both diseases are characterized by a state of chronic inflammation, and have been associated in multiple studies of children and adults.4–10 Potential

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explanations for the link between obesity and asthma include pleiotropic genetic effects,5, 11, 12 altered lung mechanics,13 resistance to treatment with inhaled corticosteroids,14–16 diet and vitamin D deficiency,17–21 coexisting morbidity (e.g., gastroesophageal reflux), and reduced or altered microbial exposure in early life (see below).

The largest and earliest source of microbial exposure in humans comes from the intestinal tract. The gut contains a large and diverse population of microbes that is, quantitatively, the most important postnatal source of microbial stimulation of the immune system.22, 23 The initial gut composition can significantly influence immune system development.24 Hence, disruption of this process early on in life at a time of dynamic changes25, 26 in the infant gut, may have long-term health effects. Both asthma27 and obesity28–30 often begin in early childhood when the gut microbiota is primarily developed. Recent studies in animal models and in humans have found a relation among gut microbiota, atopic diseases (eczema, allergic rhinitis, and asthma)31–38 and obesity.39–43 Early-life factors (i.e., diet, medications, hygiene, antioxidants, and nutrients) associated with asthma and/or obesity6 may alter the gut milieu. Vitamin D deficiency is widespread worldwide44 and has been associated with early-life wheeze, reduced asthma control20, 21, 45 and increased body mass index.46–48 Vitamin D has immune modulator properties capable of inhibiting inflammation and infections,49–51 and thus may be important in shaping the early gut microbiota. In this article, we first review recent advances in our understanding of the development and immune-modulatory properties of the gut microbiota. Next, we discuss current evidence to support a link among the gut microbiota, atopic diseases (including asthma) and obesity. Then we review the outcomes of recent probiotic trials on asthma and obesity. Finally, we review the potential link between vitamin D, asthma, obesity, and the gut microbiota.

Gut Microbiota Development

Anaerobes (particularly gram-positive Firmicutes and Actinobacteria, and gram-negative Bacteroidetes) are the predominant bacteria in the gastrointestinal tract of adult subjects.52 In humans, the gastrointestinal tract is sterile at birth. Multiple factors determine gut colonization, including bacterial characteristics, mucosal cell characteristics, mode of delivery and type of diet.36, 53, 54

The initial neonatal gut colonization is determined either by maternal flora or bacteria from the immediate environment (i.e., hospital and health care workers), depending on the mode of delivery.53, 55 The correlation between the maternal vaginal and intestinal flora may ultimately explain the correlation between the maternal and neonatal intestinal flora in children born by vaginal delivery.56–59 Neonates born by vaginal delivery are exposed to the mother's vaginal and intestinal flora as they pass through the birth canal and typically harbor communities of bacteria that resembled those of the mother's flora.55, 60 Compared with vaginal delivery, cesarean section is associated with early gut colonization with *Klebsiella* species, *Clostridium* species, and *Enterobacteriaceae* other than *E. coli*.36, 55 On the other hand, children born by cesarean section are colonized later and less frequently by *Bacteroides* species,36, 53, 55 *Bifidobacterium* species,36, 53, 55 and *E. coli*.36, 53

Data in mice have shown differences in innate immune responses between pups delivered by cesarean section and those born by vaginal delivery.61 Activation of intestinal epithelial cells (IECs) occurred only in pups born by vaginal delivery. This IECs activation occurs through contact with exogenous endotoxin acquired from maternal body fluids during vaginal delivery.61 In humans, birth by cesarean section results in alterations in the composition of the infant gut flora lasting up to at least 6 months of age.62 Risk for atopy, asthma, and allergic rhinitis63–66 has been associated with cesarean section delivery,

perhaps due to lack of exposure to the maternal vaginal and/or gut flora during normal delivery.

The type of feeding instituted early in life also influences neonatal gut colonization.[23, 36] While the data have been somewhat contradictory, in general the numbers of *Clostridium* (especially *C. difficile*), *Bacteroides*, Enterococcocci, *and Enterobacteriaceae* (especially *Klebsiella and Enterobacter*), tend to be lower and the number of Staphylococci tend to be higher in breast-fed as compared to formula-fed infants, perhaps because of higher exposure to maternal skin flora.[67] One study demonstrated that in breast-fed infants, the predominant bacterial species at age 8 weeks was *Bifidobacterium*, whereas in formula-fed neonates *Bacteroides* species predominated.[68]

In a study by Penders et al., hospitalization and premature birth were also associated with high prevalence of C. *difficile* counts similar to cesarean delivery, which may be related to hospital environmental exposure.[55] In the same study, antibiotic use in the first month of life was associated with reduced number of anaerobes such as bifidobacteria and *Bacteroides*.[55] Similarly, other studies have also found reduced number of anaerobes and higher number of enterococci, *Enterobactericeae*, and coagulase-negative staphylococci in infants from the neonatal intensive care units where antibiotics are frequently used.[69, 70] Antibiotic use in early life may lead to alterations in gut microbiota and, ultimately, abnormal development of the immune system.[71] However, it has been observed that a majority of bacterial species return to pretreatment levels relatively quickly after an antibiotic course, with the exception of a few species that fail to recover after an extended period of time.[72, 73] Although the impact of antibiotic treatment may have long-term effects, no causal association between postnatal antibiotic use and atopic diseases has been demonstrated.[74–78] The association between early antibiotic use and later development asthma[79] is likely due to reverse causation (i.e., antibiotics are more often prescribed to children predisposed to asthma).[37, 74, 80, 81] Limited evidence suggests that antibiotic use during pregnancy[82] and at the time of delivery[83] increases the risk of atopy[82] and persistent wheeze[83] in childhood. However, in the study by Penders et al., maternal antibiotic use in the last month of pregnancy was not associated with changes in the infant gut microbiota.[55]

Although bacterial colonization of the gut is completed approximately 1 week after birth, the numbers and species of bacteria fluctuate markedly during the first few months of life.[25, 26, 84] Given the relative instability[25, 26] of the intestinal colonization process during early life, any disturbance of this process may affect the microbiota and its function, potentially impacting the host's health.

Gut Microbiota and Immune Responses

Murine models suggest that bacterial gut colonization is essential for postnatal maturation of Th1 immune responses and induction of oral tolerance.[85] However, the specific microbes or groups of microbes responsible for this phenomenon have not been confidently identified. In neonate mice, the administration of antibiotics leads to alterations of the intestinal flora and impaired Th1 immune responses[86] that can be reversed by administration of *Enterococcus faecalis* (and to a lesser extent, *Lactobacillus acidophilus*) to neonates but not older mice.[87] In another study, a full intestinal flora - but not monocolonization with *Escherichia coli* or lactobacilli - supported normal oral tolerance.[88] In germ-free mice, presentation of a bacterial capsular polysaccharide (PSA) of *Bacteroides fragilis* by intestinal dendritic cells activates CD4+ T cells, elicits appropriate cytokine production, and restores adequate balance of Th1/Th2 immune responses. In rodents, some *Lactobacillus* strains have been shown to induce production of IL-12 and IFN-γ and suppress production of total IgE.[89–91]

Neonatal treatment with *Lactobacillus rhamnosus* GG have been shown to inhibit the development of experimental asthma in mice that was associated with increased Foxp3 expression and TGF-b production.92 In another study, oral treatment with live *Lactobacillus reuteri* (but not *Lactobacillus salivarius*) significantly attenuated inflammatory cell influx to the lung and decreased allergen-induced airway hyperresponsiveness in mice.93 In a follow-up study, Forsythe and his group94 demonstrated that the *Lactobacillus reuteri*-induced attenuation of allergic airway response was mediated through the suppressive function of regulatory T cells. In other murine models, stimulation with LPS increases proliferation and efficiency of Tregs through activation of their Toll-like receptors.95, 96 *In vitro* experiments show that cultured human intestinal cells produce TGF-b in response to stimulation with microbial antigens,97 and that some bifidobacterial species stimulate production of IL-10 in cord blood.98

Experimental data contributing to understanding of gut microbiota effects on immune modulation are reviewed in detail in this edition by McLoughlin and Mills. Collectively, these data suggest complex effects of gut microbiota on adaptive, innate, and T regulatory immunity that could influence asthma and obesity.

Gut Microbiota and Atopic Diseases

In cross-sectional studies, the composition of the gut flora differs between atopic and non-atopic infants.31, 32 In studies from Estonia and Sweden, atopic infants have lower counts of lactobacilli, bifidobacteria, and *Bacteroides* and higher levels of i-caproic acid (a marker of *Clostridium difficile*). as compared with non-atopic infants32,33 Although an English study found no differences in bifidobacteria or lactic acid bacteria between children (ages 3 to 5 years) with and without atopic wheeze, it had small sample size (n=66) and no additional data on stool cultures.34 Although most cross-sectional studies have examined only atopic dermatitis as an outcome, one study found increased risk of asthma with increased *C.difficile* colonization.35

Few prospective studies have examined the relation between the gut flora in early life and atopy. Among 76 Finnish children, bacterial cellular fatty acid profile and a reduced ratio of *bifidobacteria* to *clostridia* (by fluorescence in-situ hybridization [FISH]) in stool samples at age 3 weeks was associated with allergen sensitization at age 1 year.38 In a study of 324 European infants followed from birth to age 18 months, neither time to gut colonization with 11 bacterial groups nor ratio of strict anaerobic to facultative anaerobic bacteria in cultures from neonatal stool samples was associated with eczema or food allergy.36 In contrast, a study of 957 Dutch infants showed that the presence of *C. difficile* in stool samples at age 1 month (assessed by quantitative real-time PCR) was associated with increased risk of atopic dermatitis, recurrent wheeze, and allergic sensitization at age 2 years.35 In that study, early colonization with *E. coli* was associated with parental report of eczema but not with objectively diagnosed atopic dermatitis. In a Belgian study, wheezing in the first year of life was associated with increased total concentration of anaerobic bacteria and lowered concentration of *Clostridium* in stool cultures obtained at 3 weeks of age.37

Published longitudinal studies of the neonatal gut flora and atopy or atopic diseases have been limited by inadequate statistical power,36, 38 non-comprehensive microbiologic assessment of neonatal stool samples,35, 36, 38 heterogeneity of study participants,36, 38 inadequate data on maternal and neonatal diet,35, 36, 38 non-assessment of the maternal gut and vaginal flora,35, 36, 38 failure to examine modification of the effect of the gut flora on atopy by mode of delivery,35, 36, 38 and non-utilization of novel statistical approaches to explore potential microbial interactions.35, 36, 38 Moreover, studies that examined the

association between neonatal gut flora and wheeze or asthma35, 37 did not examine differences in gut microbiota between atopic and non-atopic wheeze/asthma.

Gut Microbiota and Obesity

Experimental models highlight several mechanisms connecting the gut microbiota to obesity and metabolic disorders. The recognition that gut microbiota is important in the regulation of energy extraction from the diet99 came from observation that germ-free mice (raised in the absence of microorganisms) were leaner than mice with a normal gut microbiota, even though mice with a normal gut microbiota were fed 30% less calories.100 Moreover, when germ-free mice were transplanted with gut microbiota harvested from mice with normal gut microbiota they gained 60% body fat and became insulin resistant, despite lower food intake.100 Subsequent studies also demonstrated the role of gut microbiota in regulating energy storage as triglyceride100, 101 and energy expenditure from fatty acid oxidation.101

Most recently, gut microbiota has been linked to low-grade inflammation through activation of innate immunity via the lipopolysaccharide (LPS)-toll like receptor (TLR)-4 axis.102 Cani *et al.* demonstrated that mice fed a high-fat diet for 2–4 weeks exhibited significant increase in circulating LPS levels (described as `metabolic endotoxemia'), and that these mice became obese and developed obesity-associated metabolic disorders.103, 104 Similarly, mice infused with LPS (to reach levels observed in mice that were fed a high-fat diet) also developed obesity and obesity-associated metabolic disorders.103, 104

Obesity has further been shown to be associated with altered gut microbial composition in humans39, 43 and mice.41 The gut of obese human subjects were shown to have reduced number of *Bacteroidetes* and increased number of *Firmicutes* as compared to that of their lean counterparts.39 In a few obese human subjects, an increased proportion of fecal *Bacteroidetes* was found to parallel weight loss on a hypocaloric diet during a one year intervention trial.39 Compared to lean mice, genetically obese mice (leptin-deficient mice) have reduced number of *Bacteroidetes* and increased number of *Firmicutes* isolated from the distal gut.41 Diet induced-obesity in animal models also led to increased *Mollicutes* (a class of *Firmitcutes*) that was reversible with dietary manipulation to limit weight gain.42 The fact that microbial composition is reversible with dietary modification suggests that differences in the gut composition of the obese and lean phenotypes are related to dietary factors independent of the obese state.105, 106

Data on gut microbiota and obesity in children are sparse. In a study on probiotics and allergic diseases, Kalliomäki et al. demonstrated that children who had normal weight at the age of 7 years had higher number of *Bifidobacterium* and lower number of *S. aureus* in infancy than those who were overweight at age 7 years.40

Collectively, current evidence supports a role of gut microbiota in the pathogenesis of diet-induced obesity and its related metabolic disorders, which may be reversible with diet and/or gut microbiota manipulation.

Probiotics, Atopic diseases, and Obesity

Emerging evidence suggests that a less diverse population of intestinal anaerobes in early life is associated with both atopic diseases and obesity.43, 107 Probiotics (live bacteria given orally that allow for intestinal colonization) provide a relatively safe microbial stimulus by means of cultures of organisms that are part of the gut flora of healthy infants. 108 In a study of 132 infants with family history of atopy,109 treatment with *Lactobacillus rhamnosus* strain GG before and after birth halved the risk of eczema (95% confidence interval [CI] for relative risk=0.3–0.8) but not that of allergen sensitization by age 2 years.

These results remained appreciably unchanged after four110 and seven111 years of follow-up. Interestingly, whereas the frequency of atopic sensitization at the age of 7 years was similar between the placebo and probiotic group, allergic rhinitis and asthma tended to be more common in the probiotic group,111 Administration of *lactobacilli* GG to atopic children has been associated with increased production of cytokines produced by Tregs (IL-10 and TGF-β),112, 113 and reduced severity of atopic dermatitis in as small number of infants.69 Another small clinical trial showed reduced severity of atopic dermatitis in children (aged 6–18 months) with moderate to severe disease by administration of *lactobacilli fermentum*,114 which may be mediated by increased secretion of IFN-γ by Th1 cells.115 In a recent study of 925 mother-infant pairs, prenatal administration of probiotics (containing four bacterial strains) during the last month of pregnancy and postnatal administration of pro- and pre-biotics from birth to age 6 months resulted in short-lived changes in the neonatal gut flora and reduced the incidence of atopic eczema (but had no effect on other atopic diseases or allergic sensitization) at age 2 years.116 In the same clinical trial, among the 891 children with complete follow-up at age 5 years, prenatal and postnatal probiotic supplementation did not prevent eczema, allergic rhinitis, or asthma at the age of 5 years.117 However, cesarean-delivered children supplemented with probiotics had fewer IgE-associated allergic diseases such as eczema and less allergicsensitization.117 Probiotics have not been shown to prevent asthma. In one study, probiotic administration was associated with increased wheezing in children.118

A recent meta-analysis119 of 12 clinical trials, which included some of the trials presented here, did not find a significant reduction in the symptoms or severity of eczema in children who were treated with probiotics. As pointed out by the authors, there was significant heterogeneity between studies.119 While there is still a potential role of probiotics in preventing childhood atopic dermatitis and other allergic diseases, there are many unanswered questions including strain, dosing, and timing of probiotic administration; and the population(s) most likely to benefit (e.g., neonates born by caesarean section, formula-fed infants, etc.).

Although gut microbiota manipulation in experimental models has shown promising results on controlling obesity, findings from clinical trials in humans are conflicting and potentially confounded by dietary habits, antibiotics, nutritional supplementation, and physical activity. Findings from a randomized double-blind controlled trial of pre- and post-natal administration of *Lactobacillus rhamnosus* (beginning 4 weeks before expected delivery and continuing 6 months after delivery) suggest that probiotics may modify the growth pattern of the child by restraining the excessive weight gain that occurs in the first 1 to 2 years of life but not that between age 2 to 4 years.120 Maternal probiotics-supplementation of 265 pregnant women in the first trimester did not show significant differences in either prenatal or postnatal growth rates.121, 122

Vitamin D, Gut Microbiota, Asthma and Obesity

Vitamin D deficiency has been associated with early-life wheeze, reduced asthma control20, 21, 45 and allergic diseases20, 45 and increased body mass index.46–48 In our recent review in this Journal,6 we had identified both gut microbiota and vitamin D as potential common early life exposures for asthma and obesity. It is unknown whether vitamin D deficiency affects the composition of the intestinal microbiota. While a small study suggested that decreased vitamin D intake was correlated with differences in fecal microbiota composition,123 this needs to be verified in larger cohorts.

Given the role of vitamin D in T-regulatory and dendritic cell development and function (reviewed in Griffin et al124 and in Adorini and Penna125), it is possible that the host's

vitamin D status could modify the effect of the intestinal microbiota on the immune system. For example, mice that lack the vitamin D receptor (VDR) have chronic, low-grade inflammation in the gastrointestinal tract.126 Furthermore, the absence of the VDR leads to decreased homing of T cells to the gut, resulting in further inflammation in response to normally nonpathogenic bacterial flora.126 Intestinal VDR has also been shown to be directly involved in suppression of bacteria-induced NF-κB activation.127 Wu and colleagues127 also showed that commensal bacterial colonization affects both the distribution and expression of VDR in intestinal epithelial cells, suggesting a dynamic interplay between these bacteria and the receptor.

Thus, emerging evidence suggest that the vitamin D pathway is a potentially important modifier of the effects of intestinal flora on inflammatory disorders.

Conclusions

Significant differences between the gut flora of children in industrialized and developing nations suggest that the high prevalence of allergic diseases (e.g. atopic asthma) and obesity in affluent nations may be due to changes in the intestinal flora of young infants. Although findings from cross-sectional31¯33 and birth cohort studies7, 8, 16 suggest that the maternal and neonatal gut flora influence childhood atopic diseases and obesity, these studies have been limited by small sample size,38 inadequate assessment of the composition and determinants [e.g., diet] of the neonatal gut flora,35, 38 120¯122 and absence of data on the maternal vaginal or gut flora35, 38, 120¯122.

Probiotic supplementation with specific strain or strains of microbes may be beneficial in the prevention of childhood atopic dermatitis when given in the prenatal or early postnatal life. However, the results of several trials have been inconsistent with regard to the type of probiotic used, the dosing and timing of the agent selected, and the population(s) likely to benefit. Based on current data, we cannot yet recommend probiotics as preventive treatment for atopic dermatitis, allergic sensitization, asthma, or obesity.

Recent experimental and epidemiological data suggest diverse gut colonization early in life, rather than specific microbial strain or strains, is likely the key factor in promoting normal immune development and maintaining immune homeostasis. Additionally, the role of the vitamin D receptor and the host's vitamin D status have not been accounted for in these studies. Therefore, well-designed birth cohort studies with extensive data on neonatal gut and maternal vaginal/gut microbiome, immune responses, vitamin D status and vitamin D genomics, and confounding/modifying variables (e.g., maternal and neonatal diet) are needed to further delineate the underlying immune modulation by gut microbiota important in the development and prevention of allergic diseases, asthma and obesity.

• What Do We Know?

Neonatal gut microbial colonization is important in promoting and maintaining a balanced immune response. Current data suggest that reduced or altered neonatal gut microbiota composition influence childhood atopic dermatitis. Probiotics supplementation in the prenatal or early postnatal life may be beneficial but cannot be confidently recommended for the prevention of atopic dermatitis.

• What Is Still Unknown?

There has been no fully adequate longitudinal study of the early-life gut microbiota and the development of asthma and obesity. There is no current data to support the use of probiotics in the treatment or prevention of asthma and obesity.

Abbreviations

PSA	Polysaccharide A
Foxp3	forkhead box P3
LPS	lipopolysaccharide
IL-	interleukin
TGF-	tumor growth factor
IFN-	interferon
IgE	immunoglobulin E
LPS	lipopolysaccharide
TLR-	toll like receptor
IECs	Intestinal epithelial cells
Th	T helper
VDR	Vitamin D Receptor
NF-κβ	Nuclear Factor-Kappa Beta

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TABLE 1

Studies of the association between infant intestinal or intrauterine microflora and asthma-related phenotypes in childhood.

Reference	Study type; study area	Sample size	Intestinal microflora measurement	Outcome
Bjorksten32 1999	Cross-sectional; Estonia and Sweden	62 two-year-old children	Bacterial culture	Allergic children less often colonized with lactobacilli and anaerobes; more often colonized with aerobes—coliforms and Staph aureus
Böttcher33 2000	Cross-sectional; Sweden	25 allergic and 47 nonallergic 13-month-old infants	Gas chromatography of bacterial fatty acids	Fatty acid profiles differed between allergic and nonallergic infants. Allergic infants had higher levels of i-caproic acid, (associated with Clostridium difficile)
Kalliomäki38 2001	Longitudinal; Finland	76 infants	GLC of bacterial fatty acids; FISH of bacterial cells at 3 wks and 3 months	Fatty acid profiles differed between allergic and nonallergic infants. By FISH, children with allergic sensitization at 12 months had more clostridia in infancy.
Penders35 2007	Longitudinal (KOALA); the Netherlands	957 children	RT-PCR of feces at 1 month	Presence of E coli associated with increased risk of eczema . Clostridium difficile associated with increased risk of eczema and allergic sensitization 2 yr of age.
Murray34 2005	Case-control; United Kingdom	33 case-control pairs—sensitized wheezy cases vs. non-sensitized non-wheezy controls (mean age 4.4)	PCR combined with DGGE and quantification of bifidobacteria by FISH	No difference in prevalence of lactic acid bacteria or bifidobacteria

Reference	Study type; study area	Sample size	Intestinal microflora measurement	Outcome
				between cases and controls; cases with eczema had fewer bifidobacteria.
Verhulst37 2008	Longitudinal; Belgium	154 children	Bacterial culture at 3 weeks of age	Increasing total concentration of anaerobic bacteria associated with increased odds of wheezing. Increasing concentrations of Clostridium protective of wheezing in first year of live
Forno107 2008	Case:control nested within longitudinal study ; United States	21 infants---with vs. without eczema	DGGE of stool at 1 and 4 months	Increase in diversity of gut microbiota significant in controls, but not cases
Keski-Nisula128 2009	Longitudinal; Finland	60 children	Microbial culture of amniotic fluid at time of c-section	Intrauterine growth of anaerobic bacteria and Streptococcus species associated with increased risk of doctor diagnosed asthma at age 15 to 17