



LITERATURE REVIEW

The importance of gut health in early life for long term health

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Abstract

Introduction. The gut microbiota plays an important role in the normal functioning of the host organism. The microbiota of healthy newborn affected by many factors such as prenatal exposures, maternal nutrition, mode of delivery, type of feeding, introduction to solid food and its type, geography, and antibiotics consumption; and its composition continues to mature until reaching 3 years of age. Normal gut microbiota is essential in gut health, and play an important role in our homeostasis. Therefore, gut microbiota is considered a crucial factor for proper early life development and lifelong health. Prebiotics, along with probiotics, may alter gut microbiota composition thus play a role in the prevention of various diseases associated with dysbiosis condition.

Methods. Advanced search for relevant literatures in PubMed, Cochrane, and Willey was conducted. After assessing the relevancy and eligibility, articles were selected and critically appraised.

Conclusions. Accumulating evidence from different studies has shown that the occurrence of a disease is often preceded by early alterations of the microbiota. Many studies established correlation between gut microbiota dysbiosis with diseases pathogenesis i.e obesity and other metabolic syndrome, asthma and allergies, also stress-related disorder. Prebiotic supplementation has proven to be effective in obesity, asthma and allergies management, also beneficial for immune system.

Keywords gut microbiota, gut health, gut brain axis, prebiotic

Introduction

Gut microbiota has been widely studied and well-recognized in many studies to have an important role in human health. Normal gut microbiota was not only play role in gastrointestinal health but also has great impact on proper early life development and lifelong health. Exposure to bacteria and their by-products has been shown to occur during fetal development, during delivery, and early feeding regime, and is modified by antibiotic exposure, all of which shape the microbiota composition and host's tolerance.^{1,2,3,4,5}

Microbial interventions, using prebiotics and probiotics supplementation, beginning before birth and in early infancy are widely discussed in the context of underlying mechanisms and the establishment of gut colonization as a critical early homeostatic influence. These interventions may have beneficial effect in normalize gut microbiota and prevent development of various chronic diseases in the future.

The primary aim of this literature review is to summarize the role of gut microbiota in early life and its implication on long term health. Furthermore, this review discussed about prebiotic supplementations to prevent various diseases associated with dysbiosis condition.

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Methods

Advanced search for relevant literatures in PubMed, Cochrane Library, and Wiley Online Library was conducted on prebiotics in early life and its health impact, with time windows from 2000 to 2021. After assessing the relevancy and eligibility, articles were selected and critically appraised.

Discussion

Gut health in early life

In the beginning of life, newborns intestines is in aerobic environment. This condition will only allow the facultative anaerobic microbiota to reproduce, namely the Enterobacteriaceae family. However, within a few days, the lumen intestines will turn into anaerobic and allow for the colonization of microbiota such as Bifidobacterium, Clostridium, and Bacteriodes. Later in the first few weeks, the microbiota of the newborn gut resembles the maternal skin and vaginal microbiome, with predominant bacterial such as Enterococcaceae, Streptococcaceae, Lactobacillaceae, Clostridiaceae, and Bifidobacteriaceae. Bifidobacteriaceae most likely will be majority of bacteria found in the lumen for the next few months due to its nature as milk oligosaccharide fermenters. Weaning and introduction of solid foods will mark another change in gut microbiota, which increase in abundance of Bacteroides, Clostridium, Ruminococcus, and a decrease in Bifidobacterium and Enterobacteriaceae. The human gut microbiome continues to mature until the child reaches 2 to 3 years of age, after which its composition stabilizes.^{1,2,3,4}

Gut microbiome affected by some factors such as prenatal exposures and maternal nutrition, mode of delivery, type of feeding (breastmilk vs. formula), introduction to solid food, geography, and antibiotics consumption.¹

For decades, the human fetal environment has been considered sterile under physiological conditions. But recently many studies have proven the presence of bacteria in the placenta and amniotic fluid. Prenatal exposure to fecal microbes is likely a natural part of in utero development.⁵

Other studies showed that diversity and colonization pattern of the gut microbiota were significantly associated to the mode of delivery, in which the first microbiotas of human infants are determined mainly by their mode of delivery, and differences in the bacterial populations within the infant gut are resembling to the type of microbiota that the child encounters at birth. Previous studies have demonstrated that strains originating from the maternal gut and vagina are transferred to the infant's gut in case of a vaginal delivery, while infants born by cesarean section are suggested to be initially colonized by bacteria from the environment such as from maternal skin, hospital staff or other neonates.^{6,7,8,9}

Human breast-milk covert its own microbial taxonomy that is passed on to the infant along with complex non-digestible human milk oligosaccharides (HMOs) that promote the proliferation of specific gut microbes. An infant who consumes human breast-milk is thought to ingest commensal bacteria, however, the origin of these commensals remains unclear. Bacterial transfer may happen during breastfeeding from the mother's skin, but a number of studies also support the entero-mammary pathway hypothesis, wherein bacteria from the maternal gut may reach the mammary glands via maternal dendritic cells and macrophages.^{1,5,10}

Shifts in diet can significantly alter the gut microbiota due to the presence of new substrates that promote the survival and proliferation of varied types of microbial species thus introduction of solid food will alter gut microbiome based on the type of food consumed. Clostridium group XIVa was much more abundant in the microbiotas of the children that were fed meat, while Bifidobacteria and Rothia, as well as Lactobacillus decreased over time with Bacteroides remaining the most abundant in children fed iron-only fortified cereals.¹¹

Intestinal microbiota differs by geographical location for a number of reasons. Different ethnogeographic populations may have different genetic backgrounds, regional diets, and cultural practices. Also, availability or access to better sanitation and good healthcare will also determine bacterial species inhabiting in one region.^{1,11}

Over usage of broad spectrum antibiotic became a trend to watch out for. Gut microbiota can be

severely altered if exposed to antibiotics too early in its development and/or for long periods of time. This ecological disruption combined with the decreased microbial diversity of the infant gut can provide opportunities for enteric pathogens, also may play a role in emergence of numerous diseases later in life.

Gut microbiota role and health impact in children

Gut microbiota play important roles in our homeostasis, including providing essential nutrients, metabolizing dietary fiber into short chain fatty acids, and ensuring proper development of the immune system. Therefore, gut microbiota is considered a crucial factor for proper early life development and lifelong health. Emerging evidence suggests that the colonization of microbes in the human body during early life plays a critical role in the establishment and maturation of developmental pathways and that disruption of this optimal microbial succession may contribute to lifelong and intergenerational deficits in growth and development. Dysbiosis, defines as imbalances or alterations in microbial composition or activity, can influence health and is implicated in various diseases. The factors that can disturb the balance of intestinal microbiota include lifestyle, antibiotic treatments and pathogens. Diseases such as obesity, type 2 diabetes, asthma, allergies and inflammatory bowel disease (IBD), have been associated with dysbiosis of the gut microbial ecosystem.¹²

Obesity

Obesity results from the accumulation of excess adipose tissue, which caused by behavioral and environmental factors, such as excessive consumption of energy-dense foods and a sedentary lifestyle. But studies support that intestinal microbiota take part in the development of obesity and subsequent insulin resistance.¹³

Gut microbiota metabolites, namely acetate and butyrate, bind to free fatty acid receptor 2 (FFAR2 or GPR43) and free fatty acid receptor 3 (FFAR3 or GPR41) and control eating behavior by increasing satiety and reduced food intake. Several studies also confirmed an increased Firmicutes / Bacteroidetes ratio in obese individuals. This microbiota strongly affects gastrointestinal genes expression involving

the regulation of intestinal barrier function, energy balance, the regulation of intestinal barrier function, intestinal satiety hormones release stimulation, bile acids metabolic activity modulation, absorption of nutrients by intestinal mucosa, and the generation of short-chain fatty acids (SCFAs) which contributing significantly to human physiology and metabolism.¹⁴

Type 2 Diabetes Mellitus

Although common pathway in diabetes mellitus pathogenesis has been established, few studies conducted in connection with gut microbiome shown that proliferation of some bacterial species belonging to Proteobacteria may cause the development of diabetes. The *Enterobacter cloacae* B29 isolated from the obese human faeces, can induce obesity and insulin resistance in germ-free mice model at a monocolonization manner. This result prove that gut microbiota might play a causative role in metabolic disorder, but still need further researches.¹⁵

Asthma and allergies

The atopic diseases (atopic dermatitis, allergic rhinitis, allergic conjunctivitis, anaphylaxis, and asthma) are characterized by IgE-mediated hypersensitivity to an external antigen. The hypothesis is there are critical interactions that occur between gut microbiota and immune system in early life in order to circumvent the development of hypersensitivities. Studies in animal model show that restoration of gut microbiota caused a shift toward a TH1 and TH17 dominated immune phenotype, suggesting that the gut microbiota is important in establishing the balance between the TH1/TH2 subtypes in early life. Another study by Abrahamsson *et al.*, 2014 shown that low gut microbiota diversity during the first month of life has been associated with asthma in school age.¹⁶

Gut brain axis concept

The microbiota-gut-brain axis is a bi-directional communication network encompassing the central nervous system (CNS), sympathetic and parasympathetic branches of the autonomic nervous

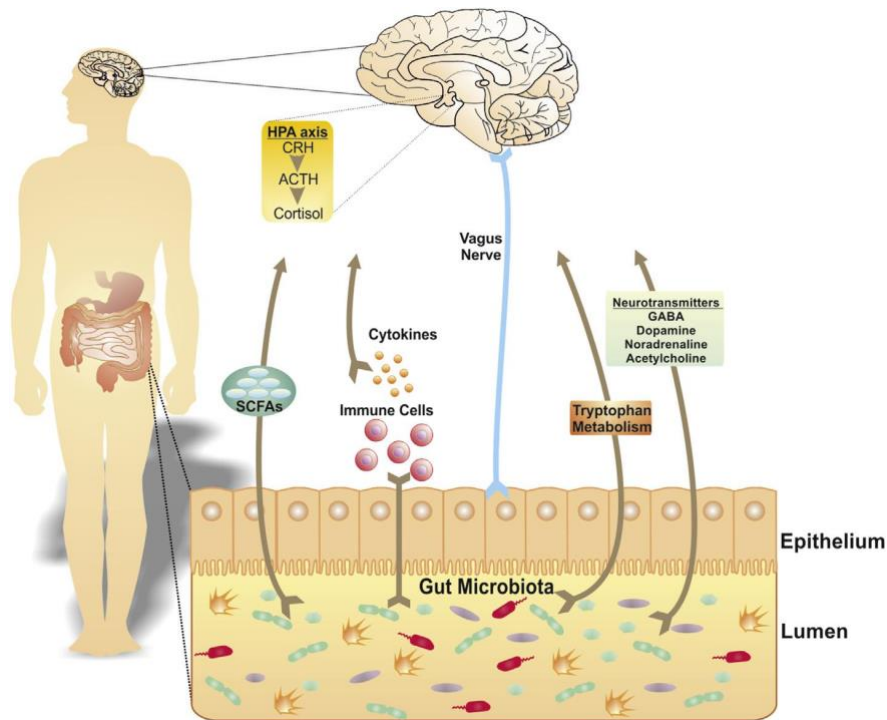


Figure 1. The microbiome-brain-gut axis and its variety of pathways.

(ACTH, adrenocorticotropin hormone; CRH, corticotropin-releasing hormone; GABA, gamma-aminobutyric acid; HPA, hypothalamic-pituitary-adrenal; SCFAs, short chain fatty acids).

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system (ANS), the enteric nervous system (ENS), neuroendocrine and neuroimmune pathways, and the gut microbiota.¹⁷

Neurodevelopment will be influenced by the individual genetic predisposition and by the influence of external factors (social, environmental, lifestyle) and dietary factors (diet, probiotics, prebiotics). There are several evidences showing mutual mechanisms between central nervous system (CNS) and gut microbiota, which involve the vagus nerve, the hypothalamic-pituitary-adrenal (HPA) axis modulation and the immune system.¹⁸ Microbiota and microbial products may potentially affect gastrointestinal homeostasis via enteric glial cells. Furthermore, enteric glial cells link microbial cues with the host's nervous system.¹⁹

The vagus nerve is able to sense the microbiota metabolites, such as peptide YY, glucagon-like peptide 1, or cholecystikinin through its afferents and to transfer this gut information to the CNS, where it will generate an adapted or inappropriate

response. Most likely CNS modulate microbiota composition by cholinergic anti-inflammatory pathway through vagus nerve fibers.¹⁸

Hypothalamic-pituitary-adrenal (HPA) axis activity is governed by the secretion of adrenocorticotrophic hormone-releasing factor and vasopressin from hypothalamus, which in turns activates the secretion of adrenocorticotrophic hormone (ACTH) from pituitary, which finally stimulates the secretion of glucocorticoids (cortisol) from the adrenal cortex. Studies, both in animal and human subjects, showed commensal microbiota, influenced by diet, had beneficial psychological effects with a decrease in serum cortisol thus plays a crucial role against the development of stress-related disorders, such as anxiety and depression.

Gut microbiota provides a broad variety of metabolites from the anaerobic fermentation of undigested dietary components, as well as endogenous material generated by the microorganism and host interaction. Gut microbes ferment dietary polysaccharides resulting in the production of monosaccharides and short chain fatty

acids (SCFA), includes acetic acid, butyric acid and propionic acid, which are important energy sources not only for the gut microbiota itself, but also for intestinal epithelial cells. Study by Ernie et al. shows that SCFA, produced by gut microbiota, is essential for microglia maintenance. Several studies also identified SCFA as inhibitors of histone deacetylases, a crucial regulator of the inactivated nuclear factor- κ B activity and pro-inflammatory innate immune responses.

Optimize gut microbiota and gut health through prebiotic

Orally supplied prebiotics and probiotics are the most common ways to influence intestinal microbiota development in early life stages. WHO (World Health Organization) described prebiotics as a nonviable food component that confers a health benefit on the host associated with modulation of the microbiota.

Potential prebiotic should fulfill some criterias. The first criteria assumes that prebiotics are not digested or just partially digested in the upper segments of the alimentary tract. As the prebiotic compound reach the colon, it will be selectively fermented by potentially beneficial bacteria, which is the second criteria. The fermentation may lead to the increased production or a change in the relative abundance of different short-chain fatty acids (SCFAs), increased stool mass, reduction of colon pH, reduction of nitrous end products and fecal enzymes, and an improvement of the immunological system, which is beneficial for the host thus fulfill the third criteria. Selective stimulation of growth and/or activity of the intestinal bacteria potentially associated with health protection and wellbeing is considered another criteria. The last criteria are a prebiotic must be able to withstand food processing conditions and remained unchanged, non-degraded, or chemically unaltered and available for bacterial metabolism in the intestine. Huebner et al. (2008) tested several commercially available prebiotics using various processing conditions. They found no significant changes of the prebiotic activity of the tested substances in various processing conditions. Prebiotics may be used as an alternative to probiotics or as an additional support for probiotics.^{21,22}

Most prebiotics are non-digestible oligosaccharides such as manno-, pectic-, soybean-, isomalto-, (trans)galacto-, and xylooligosaccharides. The vast majority of prebiotic studies have focused on inulin, fructooligosaccharides (FOS), and galactooligosaccharides (GOS). FOS and inulin usually can be found in daily diet such as onion, garlic, wheat, banana, chicory, and some cereals; while GOS have a dairy origin and are produced by the enzymatic conversion of lactose using beta-galactosidase.²⁰ The main effects of inulin, FOS, and/or GOS is that, even consumption in small amounts (0,24–0,8 gr/100 ml formula in infants or 1.5–5 gr/day in young children), able to stimulate the growth of *Bifidobacterium* and *Lactobacillus* species.²³

Based on in vitro model system investigation, prebiotic administration and propagation of beneficial bacteria will produce organic acids and resulted in a reduction in luminal pH, inhibiting growth of pathogens.²⁴

Among the fermentative products of prebiotics produced from the microbiota, short chain fatty acids (SCFAs) are studied most intensively. SCFAs are mainly composed of acetate, propionate and butyrate, and many other metabolites. SCFAs can act as energy sources absorbed through colonic mucosa. Among these, acetate is mainly metabolized in muscle, kidneys, heart, and brain. Propionate undergoes metabolism in the liver and is a neoglucogenic substrate that may inhibit cholesterol synthesis and regulate lipogenesis in adipose tissue. Meanwhile butyrate is mainly metabolized by the colonic commensal bacteria, where it acts as a preferential substrate and regulates cell growth and differentiation by different mechanisms.

There is also an evidence that prebiotic administration may modulate TH2 responses and may be beneficial in allergy cases. Study by Moro et al. 2006 and Ivakhnenko 2013 shows that administration of GOS and long-chain FOS in infant formula given in a double-blind, randomized, placebo-controlled trial in 259 infants was associated with a reduction in incidence of atopic dermatitis, wheezing and urticaria to less than 50% of the incidence in non-prebiotic formula-fed infants.²⁵

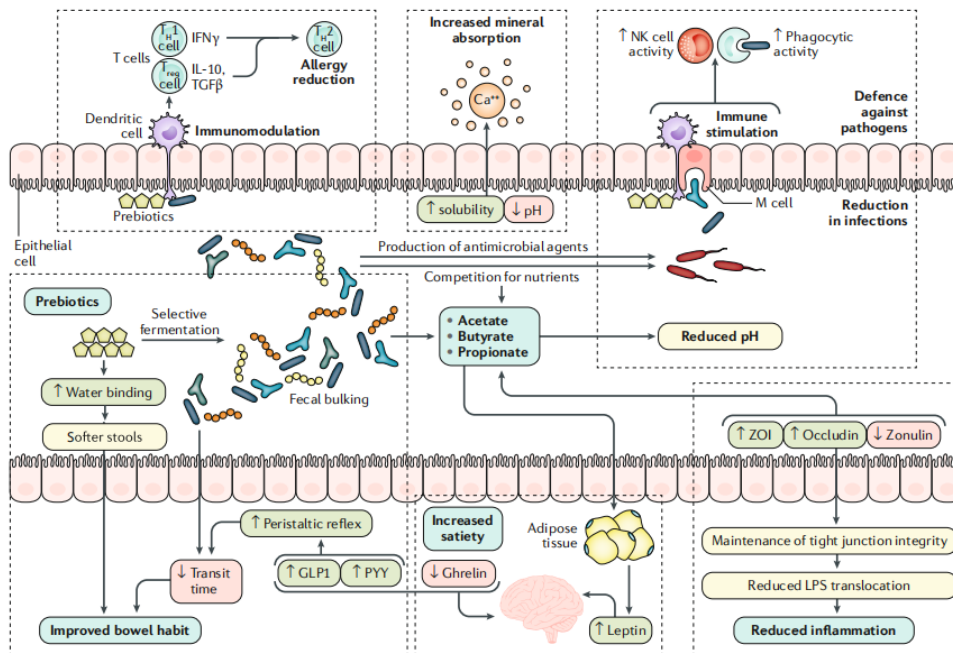


Figure 2. Prebiotic mechanism of action.

(GLP1, glucagon like peptide1; M cell, microfold cell; NK cell, natural killer cell; PYY, peptide YY; TGFβ, transforming growth factor-β; TH1 cell, type 1 T helper cell; TH2 cell, type 2 T helper cell; Treg cell, regulatory T cell; ZO1, zonula occludens 1)

Source: Sanders et al., 2019

Prebiotics enter the gut and are selectively utilized. This step increases bacterial growth and functionality of specific bacteria genus or species. Fecal bulking and improved bowel habits occur due to microbial growth. Immune regulation can be influenced by increased biomass and cell wall components of the bacteria. Metabolic products include organic acids, which lower intestinal pH and have concomitant effects upon microbial pathogens and mineral absorption. Metabolic products can also influence epithelial integrity and hormonal regulation. Bacteria that respond to prebiotic intake can influence the microbiota composition through elaboration of antimicrobial agents (for example, peptides) and competitive interactions, possibly reducing infections and bacteria containing lipopolysaccharide (LPS).

Several meta-analysis have been conducted to have better understanding about metabolic effect from prebiotic administration. Prebiotic intervention, mainly GOS and inulin, has a positive

effect on glucose homeostasis, inflammation and blood lipid profile in humans. Studies have shown that consumption by young adolescents of a mixture of FOS and inulin or GOS can result in marked increases in absorption and calcium mineralized into bone, thus may prevent osteoporosis later in life.^{25,26,27} Prebiotic administration also may induce satiety and regulate appetite because SCFAs produced by fermentation in the gut can interact with specific fatty acid receptors, FFAR2 and FFAR3, and regulate lipolysis and release of the incretin glucagon-like peptide-1.²⁴

Conclusion

Microbiota is part of gut health and has been formed since the pre-natal period. Gut microbiota in individuals is influenced by many factors, for example maternal factors, type of delivery, type of feeding, antibiotic consumption, and many else. An optimal microbiota balance in the body will provide

a good level of health, while disruption of the gut microbiota, known as dysbiosis, can cause health and immune system disorders either directly or in the future. Many studies prove that dysbiosis plays a role in the pathogenesis of IBD, asthma and allergies, obesity and other metabolic syndromes. The microbiota-gut-brain axis also emphasizes the importance of the good gut microbiome in neurodevelopmental development, as well as many studies that emphasize the relationship between the microbiota and neurological cases.

Intervention of gut microbiota can be done with supplementation of probiotics and / or prebiotics. Prebiotic administration has shown evidence of beneficial effects on the immune system, asthma and allergies, and obesity. Future studies might be needed to explain the mechanisms of actions of prebiotics and its interaction with gut microbiota, which may confer a beneficial effect on human health.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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