Pediatr Gastroenterol Hepatol Nutr. 2024 May;27(3):137-145
https://doi.org/10.5223/pghn.2024.27.3.137
pISSN 2234-8646·eISSN 2234-8840

Pediatric Gastroenterology, Hepatology & Nutrition
pghn

Review Article

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Stunting and Gut Microbiota: A Literature Review

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OPEN ACCESS

Received: Jul 18, 2023
Revised: Dec 7, 2023
Accepted: Jan 2, 2024
Published online: May 7, 2024

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Funding
None.

Conflict of Interest
The authors have no financial conflicts of interest.

ABSTRACT

Stunting, a condition characterized by impaired growth and development in children, remains a major public health concern worldwide. Over the past decade, emerging evidence has shed light on the potential role of gut microbiota modulation in stunting. Gut microbiota dysbiosis has been linked to impaired nutrient absorption, chronic inflammation, altered short-chain fatty acid production, and perturbed hormonal and signaling pathways, all of which may hinder optimal growth in children. This review aims to provide a comprehensive analysis of existing research exploring the bidirectional relationship between stunting and the gut microbiota. Although stunting can alter the gut microbial community, microbiota dysbiosis may exacerbate it, forming a vicious cycle that sustains the condition. The need for effective preventive and therapeutic strategies targeting the gut microbiota to combat stunting is also discussed. Nutritional interventions, probiotics, and prebiotics are among the most promising approaches to modulate the gut microbiota and potentially ameliorate stunting outcomes. Ultimately, a better understanding of the gut microbiota-stunting nexus is vital for guiding evidence-based interventions that can improve the growth and development trajectory of children worldwide, making substantial strides toward reducing the burden of stunting in vulnerable populations.

Keywords: Gastrointestinal microbiome; Child; Growth disorders

INTRODUCTION

Stunting is a major global health priority and the cause of almost half of all under-five mortality [1]. The World Health Organization (WHO) has set a Global Target for Reducing Childhood Stunting to 40% by 2025 [2]. A study by Bhutta et al. [3] concluded that nutritional interventions including balanced dietary protein for mothers, calcium and multiple micronutrient supplementation for mothers, folic acid supplementation, breastfeeding promotion, and vitamin A and zinc supplementation might reduce stunting by a mere 15%. This suggests that other pathophysiological mechanisms may play a role in stunting and that new therapeutic strategies are needed to improve the growth of children with stunting [4].

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Recent discoveries of the potential benefits of microbes inhabiting the gastrointestinal tract, called the gut microbiota, have gained significant attention. Previous studies demonstrated that the human gut microbiota is associated with malnutrition [5]. Persistent undernutrition may alter the normal composition of the gut microbiota and lead to dysbiosis. In turn, dysregulation of the gut microbiota disrupts many bodily functions and further exacerbates stunting [6]. This review article aims to provide an in-depth exploration of the latest research on gut microbiota as a preventive or therapeutic strategy for stunting.

OVERVIEW OF STUNTING

Stunting is defined as the condition of short stature or severe short stature based on height/length for age below –2 standard deviation (SD) on the WHO growth curve. According to the WHO, in 2020, approximately 22.2% or 149.2 million children under 5 years of age suffered from stunting. The highest prevalence of stunting was observed in Asian countries, affecting approximately 79 million children (52.9%), primarily in Southeast Asia (54.3 million children, 35%), followed by Africa (61.4 million children, 41.1%) and Latin America (5.8 million children, 3.8%) [7].

Stunting is caused by chronic malnutrition associated with low socioeconomic status, inadequate maternal nutrition and health, history of recurrent illness, and inappropriate infant and child feeding practices [8]. It typically begins with inadequate weight gain, known as weight faltering, which if not optimally addressed, will slow down linear growth as the body tries to maintain its nutritional status. This deceleration then progresses to stunting [9]. Various aspects, including poor nutrition, environmental factors, bad sanitation, maternal education levels, and maternal health, are intertwined and play roles in the cause of stunting [10]. The interaction of these factors is outlined in the WHO conceptual framework (**Fig. 1**) [10].

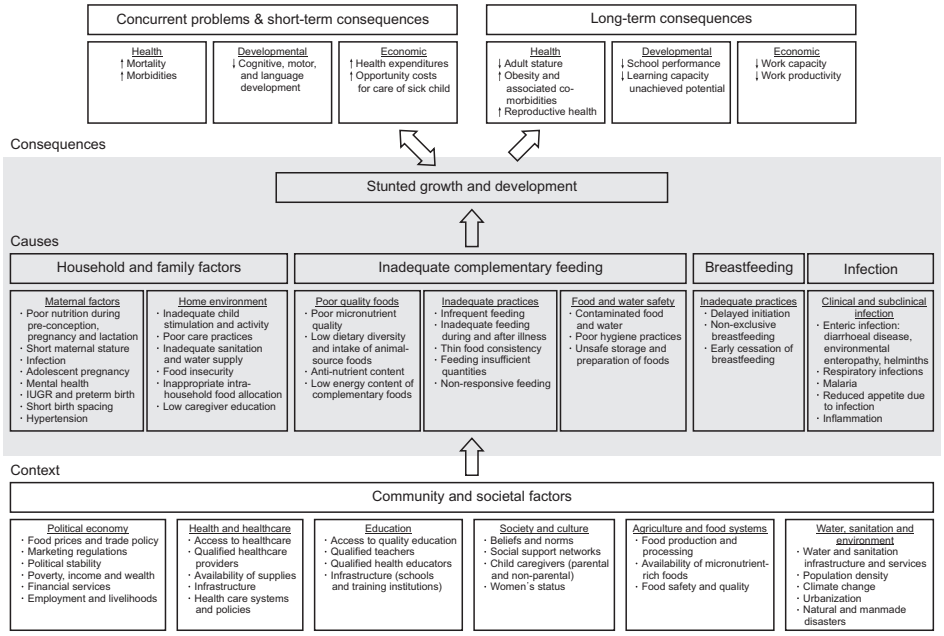

Fig. 1. World Health Organization stunting conceptual framework. Modified from World Health Organization (https://www.who.int/publications/m/item/childhood-stunting-context-causes-and-consequences-framework) [10].
IUGR: intrauterine growth restriction.

https://doi.org/10.5223/pghn.2024.27.3.137

Nutritional deficiencies during the early stages of gastrointestinal tract development can disrupt gut maturation and contribute to the occurrence of Environmental Enteric Dysfunction (EED) in infants and young children [11]. EED is characterized by structural and functional abnormalities of the small intestine, including villous atrophy or shortening, inflammatory cell infiltration, and crypt hyperplasia. Epidemiological studies suggest that continuous exposure to fecal bacteria is considered one of the primary factors contributing to the development of EED. This condition is associated with microbial and parasitic contamination of food and water caused by poor sanitation and limited public health resources. Children with EED are at risk of stunting because of deficiencies in macro- and micronutrients that are absorbed in the small intestine, such as iron, which hinders child growth [11].

GUT MICROBIOTA

Gut microbiota refers to the organisms that live in the gut, comprised mainly of bacteria, although viruses and other eukaryotes are also present [12]. There are more than 1,000 species of microbes that colonize the gut, and they play important roles in its maturation and development. Studies have shown that the formation of microbiota begins before birth and evolves as an individual grows. The initial microbiota of neonates is composed mainly of anaerobic bacteria such as Enterobacteria, Streptococci, and Enterococci. Meanwhile, the guts of older children and adolescents tend to have more colonization by *Bifidobacterium* spp. and *Faecalibacterium* spp. [13].

The gut microbiota plays an important role in an individual's physical and mental health as it affects many systems in the human body. One of the main functions of the gut microbiota is to compete with pathogenic microbes and secrete antimicrobial substances to inhibit pathogenic bacteria proliferation [13]. Additionally, several microbiota strains are also involved in the fermentation and digestion of food components in the gut, that is, the processing of nondigestible carbohydrates, short-chain fatty acids (SCFAs), fibers, dietary lipids, and the production of gasses in the gastrointestinal tract [14,15]. This process is crucial as it further modulates various activities including water and electrolyte absorption, hormone secretion, and especially immune system activation by regulating chemokines and inflammatory molecules. The microbiota is also involved in the synthesis of vitamins and minerals, the conversion of urea or ammonia to amino acids, and drug metabolism [16]. Moreover, recent studies have shown that the gut microbiota is involved in the modulation of brain neurotransmitters and signaling as they affect the vagus nerve signaling mechanism, the activation of the hypothalamus-pituitary axis, and the production of brain neurochemicals that regulate memory, mood, and learning [17].

The gut microbiota mediates child growth by participating in metabolic processes (production of SCFAs in the metabolism of human milk oligosaccharides and bile acids for lipid solubilization and absorption) and by producing insulin-like growth factor-1, which promotes organ and systemic growth and acts as a key mediator of skeletal growth. In addition, they play a role in lipopolysaccharide synthesis as potent ligands for Toll-like receptors that stimulate the secretion of hormones [15].

https://doi.org/10.5223/pghn.2024.27.3.137

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Growing evidence supports the role of commensal gut microorganisms in child growth. Children with normal growth exhibit a patterned gut microbiome within the first 1,000 days of life, known as delivery mode, breastfeeding, and complementary feeding [18]. The microbial succession affects pathways in metabolic, endocrine, and immune systems in early life, thus contributing to growth and development [19]. Immaturity of the early life gut microbiota has been found to be associated with severe acute malnutrition [20]. Altered gut microbiota characterized by decreases in *Bifidobacterium* and *Lactobacillus* species, and a high abundance of the phylum *Proteobacteria*, which are associated with diarrhea as a major cause of malnutrition in children, especially from low-income countries [21,22].

EARLY LIFE FACTORS INFLUENCING GUT MICROBIOTA COMPOSITION

The gut microbiota composition of a child changes with age and is affected by many factors, including maternal factors, delivery type, food intake, and environmental factors [23]. The delivery type (vaginal or cesarean delivery) is the first factor that determines the composition of the early gut colonizers of newborns. Studies have shown that the gut of infants born through vaginal delivery has more colonies of *Bifidobacterium* spp., the beneficial anaerobes of healthy children's gut, and are more likely to have *B. thetaiotaomicron* or *B. fragilis* compared to those born through cesarean section [24]. Other than delivery types, it has been established that breastfeeding versus formula feeding have markedly different effects on the gut microbiome. Breast milk is an excellent source of prebiotics and infant-type Bifidobacteria. Breastfed infants have been reported to have more *Bifidobacterium*, *Bacteroides* spp., and *Lactobacillus* spp. in their guts, and lower abundance of *Enterococcus* spp. and *Streptococcus* compared with formula-fed infants [23]. These bifidogenic properties of breastmilk are important for the maturation of the infant's immune system since studies have shown that reduction in these microbial properties in early life are associated with the diseases such as asthma and eczema as the child grows up. Before the age of 6 months, delivery type and breastfeeding practices are the dominant factors affecting gut microbiota composition. The introduction of complementary foods, typically starting at 6 months of age, dramatically changes the gut microbial components, slowly shifting to an adult-like microbial composition. Family foods, especially those high in proteins and dietary fibers, have been found to increase the diversity of *Lachnospiracaeae*, *Ruminococcaceae*, and *Bacteroidaceae* in the gut, which are abundant in the gut of adults [20]. Therefore, it can be concluded that vaginal birth delivery, exclusive breastfeeding, and complementary foods high in proteins and fibers are recommended for the development of healthy gut microbiota in early life.

DIFFERENCES IN GUT MICROBIOTA COMPOSITION AND DIVERSITY IN STUNTED CHILDREN

Several studies have revealed that stunted children possess a different composition of gut microbiota compared to non-stunted children. A longitudinal cohort study in India by Dinh et al. [25] concluded that a reduced number of *Bifidobacterium longum* and *Lactobacillus mucosae* and a higher number of *Desulfovibrio* spp. were associated with stunted children. The gut microbial ecosystems of stunted children were abundant in inflammogenic taxa, while those of the non-stunted group were abundant in probiotic bacteria. Other studies in Chandigarh, India, showed that the gut microbiota profile in children with malnutrition is depleted of

https://doi.org/10.5223/pghn.2024.27.3.137

Bifidobacteria [26]. A study by Gough et al. [27] in Malawi and Bangladesh demonstrated that a reduction in microbiota diversity was associated with stunting severity. Overgrowth of *Acidaminococcus* and glutamate-fermenting microbes may worsen growth deficits in malnourished children. A study using an African dataset found *Escherichia coli* (*E. coli*)/*Shigella*, and *Campylobacter* to be higher in stunted children [28]. It has been observed that among stunted children from Africa and children from Bangladesh with severe acute malnutrition, Enterobacteriaceae, which is associated with pathogenicity, is increased, together with impaired digestion, absorption, and gut inflammation. Conversely, a cross-sectional study of the pediatric population aged 3–5 years from Indonesia revealed that Enterobacteriaceae did not increase but was reduced in stunted children compared to children with normal nutritional status, with no significant difference in *Campylobacter* between stunted and normal children. These findings indicated that the gut microbiota may differ with age and diet; thus, the gut microbiota is region-specific. At the phylum level, there was a markedly lower relative abundance of Bacteroidetes and a higher relative abundance of Firmicutes in stunted children than in normal-weight children. Prevotella 9 was the most abundant genus in Indonesian children and was found to be notably lower in stunted children [28].

ASSOCIATIONS BETWEEN GUT DYSBIOSIS AND IMPAIRED GROWTH AND DEVELOPMENT

The gut microbiota is associated with food digestion, absorption, energy metabolism, and intestinal function. It may play a role in weight regulation as its constituents produce metabolites, particularly SCFAs. Persistent undernutrition during childhood may alter the normal composition of gut microbiota, leading to dysbiosis. Conversely, dysbiosis of the gut microbiota is associated with reduced plasma levels of essential amino acids and malnutrition [28].

Dysbiosis of gut microbiota in malnourished children begins with the depletion of Bifidobacteria and colonization of microbial pathogens (*E. coli*, *Streptococcus* spp., *Fusobacterium mortiferum*), which leads to diarrhea and nutrient malabsorption [15]. In addition, children with malnutrition are associated with a reduced number of *Bifidobacterium longum* and *Lactobacillus mucosae* [25]. It is unclear whether the microbial differences contribute to malnutrition or if malnutrition causes these changes. However, recent evidence supports the role of microbiota in malnutrition. Experiments using mice showed that gut microbiota with a high differential abundance of *Clostridioides innocuum* and *Bilophila wadsworthia* coupled with a low-nutrient diet enhanced malnutrition (**Fig. 2**) [29].

Another potential association between microbiota dysbiosis and stunting is the increased energy loss through fecal excretion in stunted children. Surono et al. [28] found that *Prevotella* 9, which is abundant in children with normal nutritional status, was lower in stunted children. *Prevotella* spp. are associated with long-term dietary fiber intake. Surono et al. [28] demonstrated that children with stunted growth exhibited lower intake of all macronutrients (fat, protein, carbohydrates, and dietary fiber) and energy than children with normal nutritional status. The gut microbiota ferments dietary fiber into SCFAs, which are used as an energy source in the brain, liver, muscle, and colonic epithelium. Thus, *Prevotella* may play a role in the extraction of additional energy from the diet which may benefit stunted children. The study also showed that the concentration of all individual SCFAs (acetate, propionate, *n*-valerate, *n*-butyrate), the sum of the SCFAs, and branched-chain fatty acids (*iso*-butyrate

https://doi.org/10.5223/pghn.2024.27.3.137

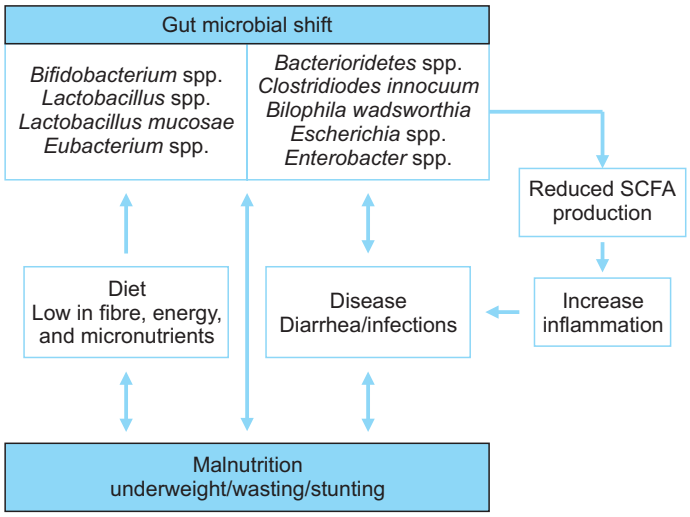

Fig. 2. Graphic summarizing possible association of the gut microbiota in childhood malnutrition and pivotal factors linked to the changes of gut microbiota (reduction in beneficial species combined with an increasing number of potentially harmful species). The direction of the arrows is correlated. Data from Iddrisu et al. (Nutrients 2021;13:2727) [23].
SCFA: short-chain fatty acid.

and *iso*-valerate) were higher in the feces of stunted children. This indicated a higher energy loss in the form of SCFAs through fecal excretion in stunted children than in children with normal nutritional status. It is estimated that approximately 5–10% of the daily energy requirement might be fulfilled by SCFAs produced by the gut microbiota [14]. Additionally, SCFAs provide other health benefits such as lowering the pH of the intestinal lumen, which inhibits the growth of pathogenic bacteria and has an anti-inflammatory effect [28]. Gut dysbiosis may be associated with lower SCFA production, increased intestinal permeability, and a higher probability of being exposed to infections. Changes in the microbiome-induced gut barrier function may affect the bioavailability and metabolism of micronutrients. These processes disturb the intestinal function and limit normal growth in children [6].

INTERVENTIONS TARGETING THE GUT MICROBIOTA TO PREVENT STUNTING

Finding ways to modulate the gut microbiota as a strategy to alleviate stunting and malnutrition is gaining interest. Three treatments, involving the use of probiotics, prebiotics, and antibiotics, have been proposed. A systematic review by Heuven et al. [30] showed that three out of four studies that administered probiotics containing mostly the Lactobacillus genus to undernourished children successfully increased their weight and height. Most of the studies delivered probiotics to children using milk drinks at a dose range of 5×10^7 to 6.5×10^9 CFU/day. Meanwhile, studies involving similar interventions using probiotics in healthy children seem to show less successful results, since only one out of three studies available showed significant positive results following the intervention [31-33]. This further emphasizes the beneficial effects of probiotics on undernourished children who are more likely to have gut dysbiosis. In addition to milk, gummies containing probiotics can be used as an alternative delivery method. A recent study by Kamil et al. [34] supplemented undernourished infants with a gummy (3 g) containing 10^{8-9} CFU of *L. plantarum* Dad-13 for 50 days and found an increase in SCFA- and butyric acid-producing colonies and a decrease in

https://doi.org/10.5223/pghn.2024.27.3.137

Enterobacteriaceae. At the end of the intervention, there was a significant increase in weight, height, weight-to-height z-score, and height-to-age z-score (p<0.05) [34].

Recent studies have shown that prebiotics shift the microbial colonies of severely malnourished children to include more *Bifidobacteria* and fewer *Enterobacteriaceae*. In a recent study by Toe et al. [35], malnourished infants were supplemented with prebiotic-enhanced solutions (Enov'Nutributter®+) for 27 days, which led to a notable increase in Bifidobacterium by 9 times and a decrease in *Enterobacteriaceae* spp. and *Bilophila* spp. compared to control subjects [35]. In addition, this study also showed that subjects in the intervention group produced higher levels of acetate and branched chain fatty acids, implying that prebiotics may have beneficial effects on the metabolic activity of malnourished infants.

Following the promising results of probiotics and prebiotics, studies are now exploring the use of synbiotics, which are combinations of probiotics and prebiotics. A recent study by Nuzhat et al. [36] showed that synbiotic supplementation in infants with severe acute malnutrition resulted in a marked increase in weight and weight-to-age z-score. Children who received synbiotics also had a mean increase in length-to-age z-score by 0.26 SD, but the data was not statistically significant (p=0.116). Interestingly, when compared to infants supplemented with probiotics (*Bifidobacterium infantis*), greater weight gain was observed. This finding was supported by the SYNERGIE trial, which also reported that *B. infantis* supplementation increased the weight of severely malnourished infants [37].

These studies suggested that the administration of prebiotics, probiotics, or their combination is a promising strategy for enhancing nutrition in malnourished children, although further research is still needed to draw conclusive recommendations. Regardless, as no serious negative effects have been reported in previous studies, the suggestion to administer prebiotics or probiotics to children with undernutrition should be considered by physicians in clinical settings.

CONCLUSION

In conclusion, stunting and the gut microbiota have a complex and intertwined relationship that perpetuates a vicious cycle. Stunting can disrupt the composition and functionality of the gut microbiota. Conversely, gut microbiota dysbiosis has been shown to be related to the impairment of nutrient metabolism, dysregulation of the immune system, alteration in SCFA production, and several hormone pathways, all contributing to further stunting. Strategies targeting gut microbiota to mitigate stunting, such as nutritional interventions, probiotics, and prebiotics, seem promising. However, further research is still needed to unravel the underlying relationship and to develop evidence-based recommendations to be applied in clinical practice.

https://doi.org/10.5223/pghn.2024.27.3.137

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