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Enferm Clin. 2020;30(S4):66–70

Enfermería Clínica

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Does gut microbiome associate with the growth of infants? A review of the literature☆

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Received 2 October 2019; accepted 17 October 2019

KEYWORDS
Microbiome;
Growth hormone;
Growth disorders;
Infant

Abstract
Objective: This review addressed recent knowledge about the association of the infant gut microbiome with postnatal growth.
Methods: This was a narrative review using sources from Medline and Scopus databases. The key terms such as microbiome ((infant gut microbiome OR gut microbiota OR intestinal microbiome OR intestinal microbiota) AND growth (stunting OR growth faltering OR growth impairment OR malnutrition OR malnourished)) were used. From 51 studies identified in the search stage, 13 studies are eligible for inclusion in this review.
Results: The included studies demonstrate the potential pathways of the gut microbiome in relation to growth. Microbiota in neonate's gut may have the ability to regulate somatotropic axis activity that can maintain growth, inducing insulin-like growth factor-1 (IGF-1) production. Besides, the gut microbiota is the key to increasing nutrients absorption that is essential to support tissue formations. Microbes in the intestine can also interact with the host's immune system protecting the barrier system to defend against the invasion of the pathogenic bacteria from the outside environment.
Conclusions: Microbes–host interactions may have a potential association with postnatal growth, although studies showing the causality are limited. Further studies observing the effect of the gut microbial colonization on infant growth is necessary.

Introduction

In 2018, UNICEF reported that approximately 149 million children under five years are stunted and this problem dominantly occurred in low-middle income countries (LMICs).[1] Stunting, termed as height-for-age Z score below −2 standard deviation of the reference population median, is

☆ Peer-review under responsibility of the scientific committee of the 1st International Conference on Nutrition and Public Health (ICNPH 2019). Full-text and the content of it is under responsibility of authors of the article.

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https://doi.org/10.1016/j.enfcli.2019.10.042
1130-8621/

associated with a high risk of morbidity and mortality, affecting the productivity of the future generation.[2] The theory of nutrition in lifecycle indicates that undernourished mother causes nutrient deficiencies of the fetus *in utero* leading to fetal growth restriction and preterm birth. As Danae et al. reported,[3] malnourished mothers are likely to have stunted children, especially in developing countries where infectious diseases are prevalent. Although many interventions in pregnant women and children have been done in addressing stunting in LMICs, the results showed a low to modest effect.[4]

Recent discoveries show that the assembly of the gut microbiota in early life has been significant in a child's healthy development. The gut microbiota is involved in metabolism pathways, such as harvesting energy, synthesizing vitamins, and regulating the immune system, preparing infants to face environmental challenges.[5] A recent review suggests that the absences of the gut microbiota potentially influences the growth trajectory by affecting the sensitivity of the growth hormones. However, studies in investigating the effect of the gut microbiota configuration on growth have been only done in the animal models. Given the fact that until recently, it is still unknown the association of the infant gut microbiota colonization on the linear growth in human, thus research in this area is essential. This article reviewed the recent knowledge to answer the hypothetical question ''does the gut microbiome relate to the growth of the infant?''.

Method

Sources of information

We searched the studies through two electronic databases (Medline and Scopus). In the very first stage, database searching, 51 studies were obtained. The criteria to include the study in this review are, studies in human or animal model, and published from the year of 2000 to current. A review article, unpublished work, and study protocol were not eligible for inclusion. In the end search, 13 studies were included (Fig. 1).

Search terms

The keywords for the search process consisted of two domains, ''microbiome'' ((infant gut microbiome OR gut microbiota OR intestinal microbiome OR intestinal microbiota) AND ''growth'' (stunting OR growth impairment OR malnutrition OR malnourished)). This literature review did not limit the type or design of the study.

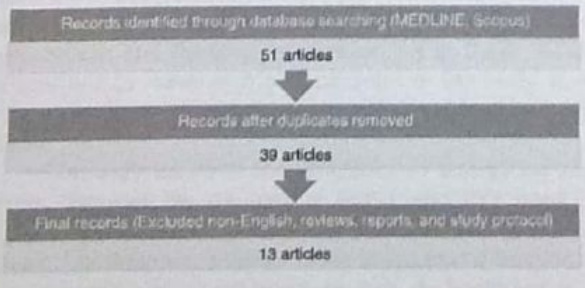

Figure 1 Flow diagram of study selection.

Result

Table 1 shows the relevant studies demonstrating the pathways of the gut microbiome in relation to growth hormones, metabolism and immune system of the hosts. There were four studies demonstrated the involvement of the gut microbiota in stimulating growth hormones.[6–9] There were six studies showed the role of the gut microbiota in metabolisms,[10–15] while three studies in relation to the immune system and inflammation.[16–18]

Discussion

Findings of this literature review suggest that the gut microbiota may be associated with postnatal growth through its effect in stimulating growth hormones, assisting nutrients metabolism, and influencing the host's immune system.

Gut microbiota and growth hormones

It is interesting to note that the intestinal health of infants may have effects on the growth through the various metabolic process, including maintaining somatotropic axis activity and driving pituitary glands to produce growth hormones (GH). A study in mice demonstrated evidence that the presence of microbiota significantly enhances the production and expressions of IGF-1 and IGFBP3.[7,19] This study also found that diet mediating by microbiota altered growth phenotype of the mice. After chronic malnutrition occurred, wild-type mice successfully adapted and resumed growth and weight, while the growth of germ-free mice was failed to recover. Another study in mammals showed that specific microbiota, such as *Lactobacillus plantarum* strain, restored juvenile growth and somatotropic sensitivity of *Drosophila melanogaster*. It is mainly due to *L. plantarum* has the capacity to modulate the host's hormonal growth signal.[6,8] In addition, colonization of microbiota is associated with an increase of bone resorption activity. From the evidence of the study in mice, growth parameter (weight and body length) and growth hormones (IGF-1 and IGFBP-3) in wild type (WT) were significantly higher than germ-free (GF) mice.[7]

Furthermore, markers for bone turnover (CTX-I and P1NP) were significantly different between GF and colonized mice, indicating that the presence of microbiota has the potential to improve bone health. Yan et al.[9] hypothesized that SCFA production in colonized mice mediated these effects. SCFAs in antibiotic-treated mice resumed the production of IGF-1 and restored bone mass to the level seen in non-antibiotic mice.[9] Although some studies support evidence of the gut microbiota role in bone growth, no evidence in the literature drawing this concept in human growth parameters. However, the association between gut microbiota and IGF-1 circulation form the previous study in animal models might provide a satisfactory explanation, offering a promising concept in stunting prevention strategies.

Table 1 Evidence that support pathways of gut microbes–growth interaction.

Author	Samples	Findings
Storelli et al. (2011)[6]	Drosophila	*L. plantarum* association was sufficient to accelerate larval development and growth by increasing InR signaling upon nutrient scarcity.
Schwarzer et al. (2016)[7]	Mice	Weight, body length, IGF-1 and IGFBP-3 of wild type (WT) were significantly higher than germ-free (GF) mice.
Schwarzer et al. (2018)[8]	Mice	The growth of conventional mice with malnutrition state was improved after a daily supplementation of *L. plantarum*^{WJ}.
Yan et al. (2016)[9]	Mice	Colonized mice had increased serum IGF-1 two-fold compared to GF siblings. Supplementation of SCFAs in antibiotic-treated mice resumed the production of IGF-1 and restored bone mass to the level seen in non-antibiotic mice.
Sjögren et al. (2012)[16]	Mice	Colonized GF mice with normal gut microbiota increase bone mass and decreased the expression of TNF-α in bone compared to CR mice.
Backhed et al. (2004)[10]	Human	Colonized adult GF mice produced a rapid increase in body fat despite reduced dietary intake.
Hua et al. (2019)[11]	Rats	The abundance of *Bifidobacterium* and *Sutterella* were positively associated with calcium absorption.
McCabe et al. (2013)[17]	Mice	Probiotics, *L. reuteri*, was shown to reduce TNF-α production in ileum and jejunum and increased bone health in male mice, but not in female mice.
Blanton et al. (2016)[12]	Mice	Immature microbiota, likely in malnourished children, altered bone morphology and metabolic abnormalities to recipient gnotobiotic mice. Microbiota from healthy infant produced greater effect on growth in weaned mice compared to undernourished donor's microbiota.
Gough et al. (2015)[13]	Human	The abundance of certain types of bacteria in the gut may be associated with linear growth deficits.
Rendina et al. (2019)[14]	Monkey	Infant of human-reared monkeys (HR) had faster weight accretion than mother-reared monkey (MR). After given solid foods, both groups showed a similar result.
Kau et al. (2015)[18]	Human and Mouse	Mice colonized with microbiota from healthy co-twin Malawian had greater IgA response than the mice colonized from the microbiota of the sibling with kwashiorkor.
Dalby et al. (2017)[15]	Mice	Low- and high-fat diet resulted in major changes in gut microbiota composition, body fat, and insulin sensitivity compared to chow diet.

Gut microbiota and nutrient metabolism

Supporting the host' metabolisms is another role of the gut microbiota underlying the hypothesis by which microbiota can contribute to the growth. Since human large intestine has limited capacity to digest certain food components, microbes help to ferment these nondigested components and derive short-chain fatty acids (SCFAs) as the end products. Acetate, butyrate, and propionate are the major microbes-derived products produced during the fermentation process of carbohydrate and protein components. Acetate can be produced by many bacteria, while propionate and butyrate tend to be produced from peptide and amino acids by certain species, such as *Faecalibacterium prausnitzii* and *Bacteroides* species. All of these SCFAs are important to many physiological roles in the body, thereby the presences of certain types of microbiota are important.

SCFAs may improve the efficiency of energy harvesting from the diet by stimulating GLP-1 and PYY production resulting in reduced glucagon production and gluconeogenesis. Consistently, another study shows that energy storage may be affected by microbial ecology. As Backhead et al.[10] demonstrated that microbial colonization of the gut promoted LPL activity and hepatic lipogenesis, thus increasing storage in adipocytes. However, to what extent the effect of energy storage induced by gut microbiome on malnourished infant is poorly understood. If malnourished children can optimize the absorption of food intake and energy storage through the presence of intestinal microbiota, it will then provide an opportunity in nutritional interventions involving the intestinal microbiota.

Additionally, SCFAs can lower pH in luminal contents and dissolve the calcium and other mineral compounds, leading to the diffusion of calcium into the cells of the intestinal mucosa. However, these metabolites are dependent on the availability of fermentable carbohydrates and protein. Thus, adequate diets for infants should be essentially provided. A study indicated that low- and high-fat diet, compared to the chow diet, significantly changed the composition of the gut microbiota,[15] which in turn, affect their functions. Furthermore, SCFAs could act as the key to increasing intestinal barrier function. These metabolites serve as an energy source for intestinal epithelial cells, protecting microorganisms from the gut across to the bloodstream. Translocation of bacteria into blood circulation may increase the risk of

systemic inflammation leading to subsequent stunting in childhood.

Gut microbiota and immune system

The intestinal microbiota is well-known to be able to communicate and establish the hosts' immune system. Recent study linked the critical role of the gut microbiota to bone health by reducing pro-inflammatory and limiting bone resorption.[17] The author argued convincingly that certain types of microbes, such as *L. reuteri*, acts as anti-inflammatory properties which can prevent bone loss caused by intestinal inflammation, although this effect was only shown in adult male mice. Consistent with an early life germ-free mice study, given colonized GF mice with normal gut microbiota at 3 weeks of age contributed to normalization of bone mass and the frequency of $CD4^+$ Tcells.[16] This finding gives the notion that the bone mass is affected by the immune system development mediated-gut microbiota. Interrelationship between gut microbiota and immunity was clearly described in a microbial transplantation study. Colonized mice with microbiota from healthy co-twin had a greater IgA response to *Verrucomicrobiaceae* than mice colonized with microbiota from kwashiorkor siblings.[18] With colonizing bacteria, the gut communicates with a barrier system to defend against the invasion of the pathogenic bacteria from outside environment through the mediation of secretory immunoglobulin A (SIgA). SIgA plays an important role in maintaining intestinal homeostasis by protecting the mucosal epithelial from outside environment pathogens.

Gut microbiota and growth of premature infants

The disturbance of the gut microbiota, normally occurs in the preterm infant, potentially cause impaired growth. Therefore, it is essential to know at which point the preterm baby can catch up on their potential growth, and what can be done to maintain the healthy development of the intestinal microbiota.

Preterm infants have greater risk of inflammation and infection as they have an underdeveloped (immature and unhealthy) gut, potentially allowing bacteria translocation. In addition, preterm infants have delayed gut microbiota colonization and they have to be immediately housed in an incubator, leading to a different bacteria abundance from that of full-term infants. Thus, preterm babies tend to have lower diversity bacteria, and a greater abundance of pathogenic bacteria, such as *Enterococcus* and *Proteobacteria* compared to full-term infants.[20] Dietary intervention may help undernourished children to diminish the detrimental effect of immature gut microbiota, improving their antibodies capacity against pathogens. Subramanian et al.[21] suggests, a prolong dietary intervention may be essential to ensure the repairing of the gut microbiota development, thus improve child's outcomes.

Type of diet, such as breastmilk, can substantially influence the microbial composition and diversity in children from 12 to 24 months. Human milk oligosaccharides (HMOs) in the mother's milk can stimulate the gut microbiota and its metabolites.[22] Matsuki et al.[23] report that *B. longum* will utilize HMOs and result in increasing organic acids production (*i.e.* acetate and lactate). Interestingly, premature infants can get this potential benefit by giving them breastmilk. A study shows that preterm infants who received breastmilk had lower intestinal permeability compared to formula-fed premature infants, thereby reducing the risk of inflammation-related diseases.[24]

Conclusions

In summary, this review shows that the gut microbiome plays a critical role in a number of physiological processes in the human body, including metabolisms, immunity, and growth hormone. Although studies in human showing the relationship between the gut microbiome and infant growth are limited, it is now clear that the involvement of the microbes in a large number of metabolic pathways can beneficially affect the postnatal growth. We suggest conducting a cohort study to further observe the effect of the gut microbial colonization on infant growth. We acknowledge the limitation of this review, which not deeply discussed the gut-brain axis that might be strongly associated with the metabolic process.

Conflict of interest

The authors declare no conflict of interest.

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