Malnutrition

Subjects: Nutrition & Dietetics

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Malnutrition refers to deficiencies, excesses or imbalances in a person's intake and/or use of energy and/or nutrients. Malnutrition in the form of undernutrition affects millions of people across the world, especially children living in developing countries. The major cause of malnutrition is inadequate access to food combined with infections causing diarrhoea. Recent advances in our understanding of the gut microbiota have shown a link between dietary intake and gut microbiota that may affect nutritional status; this suggests a potential link between the gut microbiota and malnutrition. Thus, intervention strategies that target the gut microbiota may offer an enhanced approach for combating malnutrition with respect to those traditionally employed (such as treatment with ready-to-use therapeutic food only).

severe acute malnutrition | gut microbiota | children | infants

1. Introduction

The prevalence of malnutrition in children under five years of age in developing nations remains alarming. The World Health Organization (WHO), United Nations Children's Fund (UNICEF) and the World Bank Group reported that globally in 2017, 150.8 million (22.2%) children under five years of age were stunted, with wasting threatening the lives of 7.5% (50.5 million) of children [1]. Africa and Asia are the continents most affected by such malnutrition, bearing 39% and 55% (respectively) of global stunting prevalence in children under five. It is estimated that about half of all under-five-year-old childhood deaths are as a result of stunting (chronic malnutrition), culminating in about 3 million child deaths every year [1]. The most common and immediate causes of malnutrition/undernutrition in children are inadequate dietary intake and disease (such as diarrhoea), according to the UNICEF conceptual framework of the causes of malnutrition [2], resulting in deficient growth and development. Although inadequate access to sufficient nutrition is the main cause of malnutrition, gut microbiota have also been implicated in this condition [3][4]. Alterations in the gut microbiota, characterized by increases in the phylum Proteobacteria and decreases in *Bifidobacterium* and *Lactobacillus* species, are associated with episodes of diarrhoea [5][6][7], and diarrhoea is a major causative factor in malnutrition of children, especially those in low-income countries [8][9]. The causes of malnutrition, together with strategies to counteract malnutrition, are of significant public health interest, and manipulation of the gut microbiota provides a potential opportunity for alleviation of malnutrition [10].

2. The Human Gut Microbiome in Health and Disease

2.1. In Health

The human gastrointestinal tract harbours microbial populations consisting of 10^{13}–10^{14} cells [11], but the density and composition differ markedly between compartments. In the stomach of healthy people, the bacterial load is relatively low at 10^2 colony-forming units (CFUs)/mL of contents, but rises in the small intestine to 10^2–10^4 CFUs/mL [12]. However, the highest levels (10^{12} CFUs/mL) are found in the colon, where conditions (pH 5.5–7, slow transit time, and high nutrient availability) are highly conducive for bacterial growth [13]. The colonic bacteria are mainly anaerobic [12] and carry out a range of metabolic processes, some of which are considered of benefit to the host. For example, gut microbes ferment indigestible carbohydrates, generating short-chain fatty acids (SCFAs) for the host. These SCFAs have been reported to have several health benefits to the host, including the provision of energy for epithelial cells and lowering the pH of the intestinal lumen, thus restricting growth of some pathogens [14][15] and providing an anti-inflammatory effect to the host [16]. The gut microbiota has also been observed to play an important role in absorption, storage and expenditure of energy from the diet [17][18][19] as well as synthesis of vitamins K and B12 [20][21]. Energy intake and expenditure are predominantly coordinated by the brain. The gastrointestinal tract (GI), the first site of contact with ingested food, sends important signals (through neuroendocrine and neuroimmune systems) to the brain regarding the composition and size of incoming food [22]. Furthermore, the gut microbiota is involved in the production of metabolites, including SCFAs, secondary bile acids, tryptophan and even neurotransmitters; these play an important role in gut barrier function and also in gut–brain signalling [23][24]. The gut–brain axis is important for maintaining energy balance and controlling energy expenditure, and has also been observed to impact on cognitive function [25]. Such benefits have led to a growing interest in the use of prebiotics, probiotics and other dietary modifications to modulate the gut microbiota to improve nutrition and health [26].

The role of the gut microbiota of newborns in growth and development may be dependent on the acquired microbial composition [27]. Recent metagenomic analysis of the gut microbiota of infants suggests that in addition to the composition, the functional potential of the microbiota plays a significant role in the nutritional status of the infant. For instance, the development (transmitted from the mother) of bile acid and starch metabolism bacteria may impact nutrient absorption and therefore, affect growth and development of infants [28][29]. In breastfed infants, the gut microbiota is dominated by *Bifidobacterium longum* subsp. *infantis,* which is tailored towards the metabolism of human milk oligosaccharides (HMO) [30][31]. For infants fed on formula milk, infant formulae are commonly fortified with prebiotics so as to confer similar beneficial components as those found in breastmilk [32][33][34]. Prebiotics are “substrates that are selectively utilized by host microorganisms conferring health benefits to the host” [35]. The common prebiotics used in infant formula are short-chain galacto-oligosaccharides (GOS) and long-chain fructo-oligosaccharides (FOS). These prebiotics have been shown to beneficially alter the gut microbiota of infants by selectively enhancing the growth of *Bifidobacterium* and lowering the abundance of *Enterococcus* and *Escherichia coli* [36][37]. However, GOS and FOS are structurally different from HMO [38] and so do not entirely replicate the beneficial effects of HMOs on the infant gut microbiota, for example, on a species level [34][39][40]. Nevertheless, it has been noted that an infant diet supported by prebiotic formula results in fewer infections than a placebo formula does, and so non-HMO prebiotics appear to have a positive impact in infants [41].

Probiotics are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit on the host” [42]. It is now well established that probiotics can modulate the gut microbiota of the host in a

beneficial fashion [43][44][45]. For instance, the addition of probiotics to infant formula has been known to confer numerous benefits to the infant, including the improvement of gut health and immunity, countering the growth of harmful bacteria (pathogens) in the gut and enhancing overall host immune and health status [43]. Moreover, the addition of probiotics including *Lactobacillus reuteri, Lactobacillus acidophilus, Bifidobacterium longum, Bacillus clausii* and *Bifidobacterium lactis* in infant formula has been shown to reduce risks associated with diarrhoea resulting from antibiotic use and the symptoms of colic [46][47][48]. In contrast, numerous studies have failed to find any effect of probiotics on diarrhoea outcomes in children [39][49][50]. Indeed, a recent Cochrane review based on large clinical trials with low risk of bias [51] reported little or no effect of probiotics in the reduction of diarrhoea. Such contradictory results are likely linked to the use of different probiotics and target populations. Given the contrasting evidence on the use of probiotics in the management of diarrhoea in children, there remains a need for targeted large-scale trials to follow on from the promising findings of specific probiotics that improve diarrhoea outcomes, especially in children.

2.2. In Disease

There is evidence linking the gut microbial community to a range of diseases and disorders, including inflammatory bowel disease (IBD), mood disorders, obesity, autism and psoriatic arthritis [52][53][54][55][56][57], though further research is needed to ascertain the causal link between the gut microbiota and such diseases. In some of these conditions, interventions that impact the gut microbial community have led to improvement of symptoms, further supporting a role for the microbiota [58][59][60]. An altered gut microbiota can be caused by environmental factors such as antibiotic use, diet and stress, as well as genetic factors. These changes can impair the ability of the gut microbiota to maintain good health and may allow the growth of potentially pathogenic bacteria (e.g., *Clostridioides difficile*), leading to production of metabolites that may cause a disease state in the host [61]. The relative abundance of bifidobacteria in faecal samples of normal-body-weight children was found to be higher than in overweight children of the same age bracket (7 years old). In contrast, *Staphylococcus aureus* levels were higher in the overweight children than in those with normal body weight [56]. In addition, a recent study reported an increased abundance of Firmicutes and a reduction in bifidobacteria in the gut microbiota of overweight and obese children [62]. Furthermore, it has been observed that children who became overweight/obese at age 10 years had significantly higher levels of *Bacteroides fragilis* in early infancy (3 to 6 weeks after birth) than those whose body weight remained normal [63]. These studies thus indicate that the microbial community of children may differ according to BMI, suggesting that the microbiota may have a part to play in weight gain, for example, through energy salvage. However, caution is required when considering causal links between the gut microbiota and obesity, as recent meta-analyses failed to find variations in the taxonomic microbial compositions of obese and lean adults, suggesting that microbiota differences observed in other studies could be related to factors such as diet [64][65][66]. Several other conditions, including eczema, asthma, inflammatory bowel disease (IBD) and type 1 diabetes, in infants and young children have been linked to differences in the gut microbiota. For instance, some studies show that infants with eczema have a significant reduction in relative abundance of *Bifidobacterium, Blautia, Coprococcus, Eubacterium* and *Propionibacterium* species [67] as well as a reduction in intestinal microbial population diversity [68][69]; although it is worth noting that in healthy infants, there is low microbiota diversity predominated by bifidobacteria. Moreover, an analysis of faecal microbiota of infants (1 to 11 months old) revealed

that gut microbiota alteration promotes the disfunction of $CD4^+$ T cells, which is linked to atopy in children [70]. Further, many studies have reported the gut microbiota to be altered in IBD [71][72][73][74], with an increase in Enterobacteriaceae being particularly prominent [75]. In addition, it has been found that children with prediabetes have higher levels of intestinal Bacteroidetes than healthy controls [76].

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