Paediatrica Indonesiana

p-ISSN 0030-9311; e-ISSN 2338-476X; Vol.63, No.5(2023). p.213-8; DOI: https://doi.org/10.14238/pi63.5.2023.213-8

Editorial

Intestinal microbiota and health in infants and children

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Breastfeeding is the best way to feed all infants. According to the recommendations of the *World Health Organization* (WHO), it is recommended to feed all infants exclusively with mother's milk up to the age of 6 months.[1] However, in case this is not possible, an alternative, second choice infant feeding is needed. Worldwide, cow's milk-based infant formula is the most popular and best second-choice infant feeding.

However, there are major differences in the composition of human and cow's milk. These differences concern macronutrients (differences in lactose content - human milk contains more lactose; differences in lipid and protein content - cow's milk has higher protein content) as well as micronutrients (major differences in content of sodium, potassium, etc). However, the most notable difference is the presence of oligosaccharides in human milk, as they are the third most important solid component in human milk, while oligosaccharides are virtually absent in cow's milk.[2] Human milk oligosaccharides (HMOs) are made up of five basic monosaccharides: glucose, galactose, N-ethylglucosamine, fucose, and sialic acid. Oligosaccharides have multiple functions, but their most important effect is on the composition of the gastrointestinal (GI) microbiota, stimulating the growth of bifidobacteria.[3] Members of the genus Bifidobacterium are among the first microbes to colonize the human GI tract and are believed to exert positive health benefits on their host. As a consequence, the GI microbiota composition of breast- and formula-fed infants differs.[3]

Bifidobacteria have multiple health benefits: they serve as decoy receptors for pathogens, strengthen the gut barrier function, and influence the developing immune system towards a balanced T-helper1 (TH1)/T-helper2 (TH2) composition.[4] The more bifidobacteria, the greater the health benefit. The oligosaccharides present in human milk and their stimulating effect on the amount of bifidobacteria in the GI microbiota contribute to the differences in infectious and allergic disease in breast- compared to formula-fed infants.[5,6] Bifidobacteria are among the first microbial colonizers of the intestines of newborns and play key roles in the development of their physiology, including maturation of the immune system and use of dietary components. Indeed, some nutrients, such as human milk oligosaccharides, are important drivers of bifidobacterial development.[5,6]

In order to improve the health outcome of formula-fed infants, oligosaccharides have been added to infant formula for approximately the last 20 years.[7] Galacto-oligosaccharides (GOS) and fructo-oligosaccharides (FOS) are historically the best studied, and supplementation with these seems to have a beneficial effect on infection rates.[8] However, it became recently possible to synthesize some of the ~200 HMOs chemically, via fermentation, and by enzymatic synthesis. Initially, two were added to infant formula: 2'-fucosyllactose (2'-FL) and lacto-N-neotetraose (LNnT).[9] Thus: the "human"

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oligosaccharides added to infant formula do NOT come from mother's milk; they are processed through fermentation and/or other chemical processes, but have an identical chemical structures. Therefore, the "human oligosaccharides" added to infant formula should not be called 'HMOs', as this term refers to human milk oligosaccharides. We propose to designate them as 'HMO-analogues." In the meantime, up to 7 HMO-analogues are added to infant formula. In 2016, the European Food Safety Authority (EFSA) and the United States Food and Drug Administration (FDA) have approved the safety of 2'-FL and LNnT to be added to infant formula. Multiple clinical trials have been performed and published in the meantime. Unfortunately, the designs of these clinical studies are quite different, with different inclusion criteria, duration and amount of administration of oligosaccharides.[6,8] The primary outcomes of these trials focus on safety and tolerance, which have been confirmed. Secondary outcomes suggest a decrease of infections and prescription of antibiotics. More studies are needed regarding the optimal combination, duration and dosage of HMO-analogues in infant formula.[6,8] The administration of these HMO-analogues to infant formula are "attractive" because these molecules are identical to some of the oligosaccharides in human milk. However, they remain quite costly and no study has evaluated if there is an additional clinical benefit compared to non-human prebiotics such as FOS and GOS.6,8 One study showed beneficial levels in inflammatory cytokines if 2'-FL was added to infant formula supplemented with GOS. However, strangely, the low level of 2'-FL did better than the higher level.[10]

In summary, the addition of prebiotic oligosaccharides to infant formula stimulate the development of a bifidobacteria predominant GI microbiota. Studies suggest that some clinical benefits are likely, and adverse effects have not been reported. Whether HMO-analogues offer a clinical benefit compared to non-human oligosaccharides still needs to be demonstrated.[6,8] While more studies are underway regarding the best oligosaccharides to be added and the duration and dosage of administration, there is enough evidence to recommend the supplementation of infant formula with prebiotic oligosaccharides because "more bifidobacteria bring the GI microbiota composition closer to that of the breastfed infant."

It has been demonstrated that some strains of bifidobacteria develop much better in the presence of HMO-analogues than if non-human oligosaccharides were added.[11,12] Thus, different prebiotics oligosaccharides stimulate the growth of different strains of biffidobacteria. However, no clinical studies to date have shown a clinical benefit.

Another difference between non-human oligosaccharides and HMO-analogues may be their effect on brain development, as a small proportion of the HMO-analogues are absorbed.[13,14] They interfere in brain development, resulting in better cognitive development, as demonstrated in animal studies and suggested in infants.[15-17] These benefits have yet to be studied with non-human prebiotic oligosaccharides.

Another factor that substantially determines the development of the GI microbiota composition is method of delivery: cesarean section versus spontaneous delivery.[18] The initial colonization of babies born by cesarean section is relatively close to the mother's skin microbiota, while that of the infant born by spontaneous delivery is closer to the perianal/vaginal microbiota of the mother.[18] These differences persist up to the age of one year, suggesting that there are substantial differences in microbiota composition during the development period of the immune system.

We conclude that method of delivery and feeding are the major contributors to the development of the GI microbiota of infants. Cesarean delivery and formula feeding without prebiotics are risk factors for the development of GI microbiota that is relatively poor in bifidobacteria. Bifidobacteria are predominant in the GI microbiota of breastfed infants, and have been shown to have health promoting factors.[5,6]

Conflicts of interest

FH: none
YV: has participated as a clinical investigator, and/or advisory board member, and/or consultant, and/or speaker for Abbott Nutrition, Alba Health, Arla, Ausnutria, Biogaia, By Heart, CHR Hansen, Danone, ELSE Nutrition, Friesland Campina, Nestle Health Science, Nestle Nutrition Institute, Nutricia, Mead Johnson Nutrition, Pileje, Sanulac, United Pharmaceuticals (Novalac), Yakult, Wyeth.

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