Mother’s milk and infant formula have different effects on the microbiome in babies

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Following birth and the initiation of feeding, the gastrointestinal tract of the human infant is colonized by a large diversity of micro-organisms known as the microbiome which is a complex and dynamic ecosystem consisting of several hundred bacterial species. The establishment of the gastrointestinal microbiome is a continuous and complex process which proceeds for several years through successive stages where diet plays a major role. A healthy gastrointestinal microbiome is stable and serves various useful functions such as metabolizing barely digestible polysaccharides, detoxifying toxic products, serving as a barrier against pathogens, and synthesizing vitamins. The microbiome supports the development of the host immune system. In a healthy individual, the gastrointestinal tract is in a state of eubiosis, populated by a diverse array of micro-organisms and marked by oral tolerance to commensal bacteria and benign food antigens. Therefore, it is extremely important that an effective microbiome is established in infancy as this has consequences for health maintenance and disease avoidance in later life (Adams and Gutierrez, 2018).

The subsequent development of the microbiome in infants is strongly influenced by the feeding regime. Infants are generally fed on one of two regimes, breast milk or formula milk. Breast-fed infants develop a more stable and uniform population in the microbiome when compared to the formula-fed infants.

Among breast-fed infants, Bifidobacteria and particularly B. longum, B. infantis and B. breve can reach up to 60–90% of the total faecal microbiota. In formula-fed infants, the microbiome is more complex. In particular, the incidences of Clostridium and Streptococcus species, Bacillus subtilis, Bacteroides vulgatus, Veillonella parvula, Lactobacillus acidophilus, Escherichia coli, Pseudomonas aeruginosa, Enterococcus faecalis and Atopobium atrohaemolyticum are significantly higher in formula-fed infants than those in the breast-fed infants. There was also a delayed colonization by Bifidobacteria. Relatively small amounts of formula supplementation to breast-fed infants will result in shifts from a breast-fed to a formula-fed pattern characterized by a wider spectrum of micro-organisms in the microbiome (Guardadelli and Salvator, 2012; Angelakis and Raoult, 2018).

After weaning, the Bifidobacteria flora is...
outcompeted by adult-type microorganisms, represented mainly by bacteria in the genera Bacteroides, Prevotella, Ruminococcus, Clostridium, and Veillonella. Eventually, by about three years of age, a typical adult-like gut microbiota is established (Tanaka and Nakayama, 2017).

Breast milk is clearly the most suitable food for human babies and an additional benefit from human milk is its ability to ensure development of an effective microbiome. In addition to the essential nutrients, carbohydrates, fats and proteins, human milk contains significant quantities of special oligosaccharides, known collectively as human milk oligosaccharides (HMOs). These HMOs do not provide energy to the infant as they are poorly digested in the small intestine and mostly reach the colon, where they are fermented, mainly by Bifidobacterium, to produce short-chain fatty acids. The HMOs are a key guide to support the assembly of a healthy microbiome in the infant, dominated by beneficial micro-organisms such as Bifidobacteria.

Establishment of an effective microbiome through breast-feeding is very important as it is now recognised that deregulation of the microbiome also known as dysbiosis (an imbalance between commensal and pathogenic organisms), is associated with the development of various diseases. These are, diarrhoea and necrotizing enterocolitis in the newborn, allergic and autoimmune diseases in childhood, including coeliac disease, type 1 diabetes and atopic dermatitis. Later in life, there is a risk of inflammatory bowel diseases, irritable bowel syndrome, cardiovascular diseases, obesity, type-2 diabetes and brain disorders. Consequently, the gastrointestinal microbiome is a key mediator between exposures to internal and external environmental factors, including diet and stress (Guardadali and Salvatori, 2012).

In addition to their prebiotic effects in supporting beneficial bacteria in the microbiome, HMOs also directly deter colonization by pathogens (not only bacteria but also viruses) by acting as anti-adhesive antimicrobials. Many cell-surface glycans function as pathogen receptors or co-receptors. The structure of some HMOs is so similar to these receptors that they can act as decoys. The pathogens or virulence factors such as toxins bind to the soluble HMOs instead of the cellular receptors, and are therefore carried harmlessly through the gastrointestinal tract rather than triggering an infection. This protective mechanism has been reported for several diarrhoea causing pathogens such as Campylobacter jejuni and Salmonella enterica, but also against pathogenic Escherichia coli, Pseudomonas aeruginosa and Streptococcus pneumoniae. Fucosylated HMOs such as 2'-fucosyllactose and 3'-fucosyllactose are particularly adept at reducing the risk of norovirus infections, which are among the most common intestinal infections in infants worldwide. Human milk oligosaccharides also show antimicrobial activity against pathogenic Staphylococcus aureus and Acinetobacter baumannii, the major source of nosocomial infections, suggesting HMOs could be used therapeutically or prophylactically as well as nutritionally (Craft and Townsend, 2017). In a clinical trial, infants fed on formula supplemented with 2'-fucosyllactose and lacto-N-neotetraose suffered significantly lower rates of respiratory tract infections than infants in the control group receiving formula without HMOs (Puccio et al., 2016).

Obesity is another major modern health issue. The development of obesity in relation to infant feeding regimes as (1) only breast-fed, (2) mixed-fed, or (3) only formula-fed was studied in a large Canadian cohort (Rossiter et al., 2015). A higher proportion of children given formula in early infancy were overweight or obese compared to children who received formula in later infancy or who never received formula. When classified by feeding type, there was no difference in the proportion of obese children in the only breastfed or mixed-fed groups; however, the proportion of obese children in the group fed only formula was higher.

In another comparative study between infants fed exclusively breast milk and those fed either combination diets or exclusively formula there were differences in the microbiome (Madan et al., 2016). Infants fed both breast milk and formula had intestinal microbial communities that were similar to those fed exclusively formula and relatively distinct from those fed exclusively breast milk.

Early feeding has the potential to exert lasting effects on the microbiome and these effects may be one mechanism for the health benefits of breast feeding on childhood and lifelong health.
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Mature human milk contains 5–15 g oligosaccharides/L, representing the third largest solid component after lactose and lipids. The most abundant HMO is 2′-fucosyllactose which ranges from 0.06 to 4.65 g/L. It is also important to note that oligosaccharides in bovine milk are very low, only 0.03–0.06 g/L (Urashima et al., 2013). Therefore, HMOs are present at up to 250-fold higher concentrations in human milk than the oligosaccharides that are found in bovine milk which is commonly used in formula feeds. Clearly an infant fed on breast milk has inevitably received a much higher level of valuable HMOs than an infant fed formula on.

A logical step would be to improve infant formula by the inclusion of some HMOs. The addition of the HMO 2′-fucosyllactose to formula feeds were able to reduce cytokine levels (Goehringer et al., 2016). Cytokines are cell-signalling molecules that regulate both the innate and adaptive immune responses and guide the differentiation and development of immune cells. Infants fed 2′-fucosyllactose–fortified formulae exhibited innate cytokine profiles that were intermediate between breastfed and control formula-fed infants and were more like breast-fed infants. Breast-fed infants and infants fed experimental formulae with 2′-fucosyllactose were different but had 29–85% lower concentrations of plasma inflammatory cytokines than did infants fed the control formula. In this study feeding a single HMO 2′-fucosyllactose, in an infant formula, modified innate and adaptive immune profiles to be more like that of a breast-fed group. Fortification of formula feed with 2′-fucosyllactose supported aspects of immune development and regulation similar to that in a breast-fed reference group of infants.

Further studies have been carried out with human infants fed formula supplemented with two HMOs: 2′-fucosyllactose (1 g/L) and lacto-N-neotetraose (0.5 g/L). The results demonstrated that the global microbiome composition of infants fed formulae with 2′-fucosyllactose and lacto-N-neotetraose was significantly different to that of infants fed non-supplemented formula and closer to that of breast-fed infants at three months of age (Donovan and Comstock, 2016). This is additional support for the concept that HMOs play an important role in the development of an effective microbiome in infants.

Until recently, the inclusion of HMOs in formula milk was restricted to research trials because it was not possible to obtain HMOs for general inclusion in formula milk. In 2016 however, the first infant formula containing 2′-fucosyllactose reached the US market, followed in 2017 by a product supplemented with 2′-fucosyllactose and lacto-N-neotetraose in Spain. Nowadays, 2′-fucosyllactose can be produced at the multi-ton scale and is provided as a supplement for infant formula, medical nutrition and general nutrition. Jennewein Biotechnologie GmbH, located in Germany, has developed a unique HMO production process based on bacterial fermentation, which allows the industrial-scale synthesis of various HMOs including 2′-fucosyllactose. The family founded company is a pioneer in HMO production, and the biotechnology-derived 2′-fucosyllactose product was awarded US Food and Drug Adminstration (FDA) generally regarded as safe (GRAS) status in 2015.

References:


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