Prebiotics in infant formulae
Could we modify the immune response?

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ABSTRACT: The intestinal micro flora is an important physiologic factor in the development of the immune system. Human milk oligosaccharides have been shown to stimulate selectively the growth of Bifidobacteria and Lactobacilli in the intestine. In the last few years several attempts have been made to obtain a similar microbiota in formula-fed infants. One of the approaches is to supply the potential helpful microbiota with selective nutrients (prebiotics). Prebiotics are substances that are not absorbed through the small intestine and are fermented by colonic bacteria. A prebiotic mixture from galactooligosaccharides and fructooligosaccharides has been used to mimic the effect of human milk oligosaccharides. It has been demonstrated that such a mixture increases significantly the number of bifidobacteria in a dose-related way and reduces the number of pathogens when compared with a group in infants fed an unsupplemented formula. A few recent studies have been able to show clinical benefits with the use of a prebiotic mixture in infant formulae, decreasing the risk of developing atopic dermatitis in high risk infants and reducing the incidence of intestinal as well as upper airway infections in the first year of life. It is logical to speculate that this dual action can be through the modification of the intestinal flora. Although these initial promising results, additional studies are needed in order to confirm the evidence of clinical benefit.

Newborn babies and infants possess a functional but immature immune system which has the function of protecting against infections. Breast milk contains a number of biological, active compounds that can improve the infant's immune system. This exiting knowledge on immunomodulation by nutrient ingredients has been translated to incorporate these ingredients into the currently available infant formulae. The present article reviews the strength of evidence regarding the immune-stimulating effects of prebiotics and how they are used in current infant formulae.

DEVELOPMENT OF THE INFANT IMMUNE SYSTEM

At birth the gastrointestinal (GI) tract is essentially germ-free, with intestinal colonization occurring during birth or shortly afterwards. Within the first days of life, mucosal surfaces of the gastrointestinal as well as the respiratory tract become colonized with bacteriae. The lymphoid system is not yet mature, although it is developed. Lymphocytes T and B are naive. Activation of T lymphocytes results in a type TH2 response, that is production of cytokines IL-4 and IL-5 and very low TH1 cytokine γ-interferon. Although after birth there is an immense exposition to a wide spectrum of commensal and pathogenic microorganisms, the immune system does not respond to every stimulus. The corresponding pathogen-associated molecular patterns are recognized by receptors of the immune system, and this shapes the direction of the immune system's development through childhood to adulthood. During pregnancy, the immune system of the fetus coexists with the mother's immune system. After birth, the immune system must switch in order to protect the infant against pathogens and to develop tolerance to harmless non-self antigens, such as food antigens. Until this immune defence is already set, infants are at risk for serious infection. On the other side, the immune system is tightly controlled by its own regulatory network to prevent inappropriate immune reactions from resulting in pathologic conditions. If this system fails, the result can be allergy or autoimmune disease.

The close relationship between colonic micro flora and host cells has the central role in health and disease. Dietary modulaton is important for improved gut health, especially during the highly-sensitive stage of infancy (1-3). Marked differences in the composition of gut flora have been recognized in response to infant feeding regimen. Differences in gut micro flora composition and incidence of infections exist between breast-fed and formula-fed infants, with the former thought to have improved protection.

Although there are different elements in infant feeding that can play a role we will only discuss the role of prebiotics, especially when added to infant formulae.

BREAST MILK AND DEFENCE AGAINST INFECTIONS

Breast milk confers passive immunity to the newborn. Breast milk contains 0.4 to 1.0 g/L secretory IgA, antimicrobial protein (lactoferrine, lysozyme), leukocytes, cytokines and chemokines, hormones, fatty acids, oligosaccharides, as well as minerals, vitamins and other components that may contribute to the defence against infections. Breast milk contains at least 80 different oligosaccharides. Many of them act as receptor analogous that inhibit the binding of bacterial and viral pathogens or toxins to gut epithelial cells. Oligosaccharides also promote the proliferation of commensal Bifidobacterium spp and lactobacilli in the intestinal tract (4).

PREBIOTICS

Two different approaches towards modifying the development and balance of intestinal micro flora can be taken: one is the addition of live bacteria and bifidobacteria (probiotics) and the other is the addition of oligosaccharides that survive passage through the small intestine and reach the colon where they are used by colonic bacteria (prebiotics). A prebiotic is a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon (5). For a food ingredient to be considered a prebiotic, it must: 1) neither be hydrolyzed nor absorbed in the upper part of the GI tract; 2) be a selective substrate for one or a few beneficial bacteria in the colon; 3) consequently be able to alter the colonic micro flora towards a healthier composition. Although any dietary component that reaches the colon intact is a potential prebiotic, most of the interest is aimed to non-digestible oligosaccharides (6). Fructo-oligosaccharides and galacto-oligosaccharides have demonstrated beneficial effects on the intestinal micro flora. Oligosaccharides are sugars containing between two and twenty units. They can occur naturally in fruits and vegetables or be produced by the hydrolysis of polysaccharides. As prebiotics are not digestible, they are fully available to the bacteria that reside in the intestinal tract and interact with the intestinal microbiota.
Prebiotic consumption shifts the composition of the intestinal microbiota towards those associated with a healthy condition in the host. As the composition of the microbiota is modified, the types of bacterial metabolites into which prebiotics are converted are also modified e.g. producing a greater amount of short chain fatty acids. Many of these metabolites are absorbed into the blood of the most enter the systemic circulation interacting with many physiologic processes. In this way prebiotics act a) improving intestinal transit time (7); b) increasing the absorption of minerals, mainly calcium and manganese (8), c) anticancer effects, mainly in the prevention or progression of colon cancer (9, 10); d) modifying lipid metabolism (11) and e) modulating various systemic immune markers (12).

PREBIOTICS AND HUMAN MILK

Although in normal circumstances the newborn baby is inoculated by the mother’s flora when passing through the birth canal, the main factor contributing to the establishment of a particular micro flora is the type of feeding. If the baby is breast-fed bifidobacteria become soon predominant. This situation persists till weaning. On the contrary, formula-fed babies harbour a varied flora consisting of Bifidobacteria, Escherichia coli, and Bacteroides (13). When complementary feeding is introduced a diversification of the flora occurs (Figure 1).

Human milk stimulates the growth of Bifidobacteria because of high oligosaccharide content (10-12 g/L). Human milk oligosaccharides are a combination of five monosaccharides: glucose, galactose, sialic acid, fucose, and N-acetyl-glycosamine. They are synthesized in the mammalian gland in sequences of 5 to 10 monosaccharides (14). These oligosaccharides are predominantly neutral, low molecular weight molecules, and depending on the Lewis blood group of the mother. More recently it has been reported that human milk already has a probiotic effect as it also contents lactic acid bacteriae. In this sense we could more properly talk of the symbiotic effect of human milk (15, 16).

PREBIOTICS IN INFANT FEEDINGS

Inuline and oligofructose are safe inducers of a Bifidus flora, so it appears clear its use in infant feedings (17-19). While in Europe these are the most common prebiotics added to infant formulae (10 percent inulin with 5-60 fructose monomers and 90 percent galactooligosaccharides 2-7 monomers), in Japan they use isomaltooligosaccharides and xyloooligosaccharides.

The prebiotic formulae are reported to have multiple effects mediated through changes in the flora, the immune system and other mechanisms (20, 21). It has been clearly demonstrated an increase in the Bifidobacteria and Lactobacilli content in faeces after 28 days of supplementation, in a dose-related mode (with 0.4 and 0.8 g/dL) to the levels seen in breast-fed infants (Figure 2) (22, 23).

This effect could be also observed in premature infants. This change in flora was correlated with an increase in the metabolic activity (pH, lactate and short chain fatty acids production) (24). Using molecular biology techniques it was observed that the types of Bifidobacteria and Lactobacilli corresponded with the patterns seen in breastfeedings (25). This shift in micro flora was accompanied by a reduction in potential pathogens. The Scientific Committee on Food of the European Union considered safe the addition of this oligosaccharide mixture (GOS 90 percent + FOS 10 percent) at 0.8 g/dL, when added to an infant formula (26). The Committee on Nutrition of the European Society of Pediatric Gastroenterology, Hepatology and Nutrition pointed in 2004 that at that moment no conclusive recommendation could be done on the benefits of the addition of a prebiotic mixture to an infant formula. They suggested to perform prospective clinical trials designed to show the clinical benefits of such an approach (27).

Since then several new trials have been published (Table 1).

The putative effect of prebiotic formula on the immune system has been demonstrated by recent studies on the incidence of infections during the first year of life and on atopic dermatitis. In a prospective, randomized, placebo-controlled open trial, infants receiving the prebiotics mixture during 12 months have significantly fewer episodes of GI and respiratory tract infections (28, 29). In other study in infants at risk for atopy the use of the prebiotics formula demonstrated a protective effect at 6 months (30).

PREBIOTICS IN INFANT FEEDINGS

Table 1. Clinical trial on prebiotic supplementation in infant formulae

<table>
<thead>
<tr>
<th>Lactobacillus (GOS)</th>
<th>Number of infants</th>
<th>Subgroup</th>
<th>Prebiotic mixture</th>
<th>Length of the study</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast milk (GOS)</td>
<td>191 (12-48)</td>
<td>MF 60</td>
<td>GOS + FOS 0.8 g/dL</td>
<td>6 months</td>
<td>No effect on intestinal flora.</td>
</tr>
<tr>
<td>Infant (GOS)</td>
<td>206</td>
<td>MF 90</td>
<td>GOS + FOS 0.8 g/dL</td>
<td>6 months</td>
<td>No effect on intestinal flora.</td>
</tr>
<tr>
<td>Infant (GOS)</td>
<td>201</td>
<td>MF 60</td>
<td>GOS + FOS 0.8 g/dL</td>
<td>6 months</td>
<td>No effect on intestinal flora.</td>
</tr>
</tbody>
</table>

Figure 1. Intestinal colonization according to age.

Figure 2. Bifidogenic effect of a prebiotic mixture in an infant formula (modified from Moro et al., with authorization).

Figure 7. Log number bacteria/g of faeces.

Table 1. Clinical trial on prebiotic supplementation in infant formulae.


In a follow-up to 2 years, there was still a lower incidence of allergic manifestations in a group of 134 infants who received either a prebiotic supplemented formula or a standard one (31). Potential mechanisms of the prebiotic effect may be by improving gut barrier and also an enhanced faecal secretory IgA levels. Inulin and oligofructose have been also studied in special infant formulae as well as in weaning foods in toddlers, but they have a lower interest than in the case of infant formula. It is logical to speculate that this dual action can be through the modification of the intestinal flora. Although these initial promising results, additional studies are needed in order to confirm the evidence of clinical benefit.

CONCLUSIONS

It have been well established that a prebiotic mixture in infant formula has a bifidogenic effect. A few recent clinical studies report encouraging data on immune mediated effects of prebiotic supplementation: less GI and respiratory infections, less atopic dermatitis at an early age. It is probable that both effects are related. Nevertheless additional studies are needed in order to confirm the evidence of this promising data.

HIGHLIGHTS

- It has been demonstrated that a mixture of fructo-oligosaccharides and galacto-oligosaccharides added to an infant formula (0.8 g/dL) increases significantly the number of bifidobacteria in faeces in a dose-related way and reduces the number of pathogens when compared with unsupplemented formula.
- Clinical studies report encouraging data on immune mediated effects of prebiotic supplementation: less gastrointestinal and respiratory infections, less atopic dermatitis at an early age.

REFERENCES AND NOTES


Readers interested in a complete list of references are kindly invited to write to the author at jmoreno.hdoc@salud.madrid.org