Specific nutritional concepts & clinical evidence in the management of allergy

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Human milk immunological benefits

Human milk is universally acknowledged as the premium source of complete nourishment for young infants; its benefits include optimizing maturation and growth, preventing allergies and infections, and enhancing the development of the brain and eyes. The manifold beneficial immunological properties of human milk vastly outweigh any hypothetical negative impact as one potential route for allergic sensitization. To this day, human milk research continues to provide new insights into the health benefits of this amazing food.

Human milk contains many bioactive components that contribute to immune maturation, inducing tolerance and regulating inflammatory responses in newborns.[1] Human milk contains diverse proteins and enzymes with antimicrobial (eg, immunoglobulins, lactoferrin, lysozyme), immunodevelopmental (eg, macrophages, neutrophils, lymphocytes), and anti-inflammatory (eg, cytokines, adhesion molecules, long-chain polyunsaturated fatty acids) properties.[1] It also constitutes the principal source of allergen exposure and immunomodulation for breast-fed infants in the first year of life. For example, TGFβ and allergen-immunoglobulin G (IgG) immune complexes in human milk are potent inducers of oral tolerance; these complexes have been found to be important in the primary prevention of asthma.[2] Nevertheless, maternal consumption of an allergen does not guarantee that it will appear in her milk; ovalbumin is absent from the milk of 25% of mothers who have ingested egg.[3] Compared to formula feeds, human milk also promotes the colonization of *Bifidobacteria*, *Lactobacilli*, and *Streptococci* in the infant gut, resulting in a more diverse and healthier intestinal microbiota.[4]

Human milk oligosaccharides

Soluble human milk oligosaccharides (HMOS) are unique constituents abundant in human milk, that have aroused much recent research interest due to their important structural, functional and metabolic roles in nutrition. In particular, HMOS have a prebiotic effect in stimulating the growth and activity of certain gut microbes that are known to confer health benefits. A normal well-balanced gut microbiota significantly improves stool quality and reduces the risk of gastroenteritis, infections, and allergic symptoms.[5]

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Other studies have revealed that HMOS also have direct immumodulatory and anti-inflammatory properties. In vitro, HMOS is involved in skewing the differentiation of T cells derived from cord blood, suggesting a possible role in balancing the immune system in breast-fed infants.[6] Specific HMOS also inhibit monocyte, lymphocyte and neutrophil adhesion to endothelial cells to regulate inflammatory reactions in the event of excessive leukocyte infiltration.[7] HMOS can also suppress Th-2-mediated responses to normalize allergen-specific immune responses in newborns who are at risk of atopy.[8] Emerging evidence suggests that HMOS may also protect against enteric and other infectious diseases. One type of HMOS, 2-linked fucosylated oligosaccharide (2-FOS), has significant anti-infective properties, and contributes to cellular and humoral immunity in breast-fed infants.[9] A cohort of Mexican infants who were fed human milk containing a higher ratio of 2-FOS, had a lower incidence of *Escherichia coli*-induced infection than infants who consumed human milk with a lower 2-FOS content.[10] Collectively, these immumodulatory features suggest that enhancing the diet of non-breast-fed infants with the right type and quantity of prebiotic oligosaccharides can be a potential strategy to prevent inflammation and infectious diseases.

From Danone Research – Centre for Specialised Nutrition, Singapore

Hypoallergenic infant formulas

Dietary interventions to prevent and treat allergic disease in formula-fed infants have conventionally been based on allergen avoidance and nutritional modification. Partially hydrolyzed formulas are favored for preventing allergies, while extensively hydrolyzed formulas (eHF) and amino-acid-based formulas (AAF) can be used therapeutically. Since such products are expensive, soya formulas provide an affordable alternative for treating infants aged 6 months or above, having first verified tolerance.

In mice orally sensitized to cow milk, acute allergic skin reactions following cutaneous exposure to whey proteins diminish with increasing degrees of whey hydrolyzation.[11] eHF has been investigated as a suitable alternative to cow milk formulas for infants with cow milk protein allergy (CMPA). Oral challenge with the extensively hydrolyzed whey formula, Nutrilon Pepti, was tolerated by 97% of infants with known CMPA.[12] As well as being well-tolerated, eHF provided nutritional support comparable to standard whey formula, as shown by similar weight and length increments of infants at 13 weeks.[13] eHF also improved allergy symptoms involving the skin, respiratory and gastrointestinal tracts of infants with CMPA, without compromising their growth,[14] and substantially reduced their prevalence and severity of eczema and colic.

Nonetheless, a small proportion of infants develop intolerance to hydrolyzed protein formulas, which usually manifests in acute gastrointestinal symptoms; such infants suffer from bloody stools, emesis, diarrhea, irritability, and failure to gain weight. Infants with such symptoms may benefit from an AAF, such as Neocate hypoallergenic infant formula. Hydrolyzate-intolerant infants treated with Neocate for 14 days had improved symptoms, with significantly fewer stools per day (p =0.041), and less persistent crying (p =0.003) and vomiting (p =0.028).[15] Other infants treated with Neocate showed improved weight gain.[16]

AAF may provide the only therapeutic choice for managing multiple food allergy (MFA) with hypersensitivity to two or more dietary antigens,[17] particularly non-IgE-mediated MFA, which is difficult to manage and may only respond to food elimination. Infants with atopic dermatitis, gastro-esophageal reflux, eosinophilic esophagitis, and short bowel syndrome may also benefit from hypoallergenic AAF.

Prebiotic oligosaccharides mixture

Because HMOS are not commercially available, a synergistic mixture of two prebiotic oligosaccharides – short-chain galacto-oligosaccharides (scGOS) and long chain fructo-oligosaccharides (lcFOS) – has been developed to emulate this natural human milk fraction. This specific mixture comprising 90% scGOS and 10% lcFOS (scGOS/lcFOS) mimics the size, linkage and, partially, the building blocks of HMOS.[18] In independent clinical studies, scGOS/lcFOS supplementation selectively increased *Bifidobacteria* in the gut of premature and term infants, and toddlers. In other studies, scGOS/lcFOS significantly reduced the growth of potential pathogenic bacterial strains, lowered pH, and promoted an acetate-dominant short-chain fatty acid pattern in the gut. These beneficial changes in the colonic environment could result in improved stool consistency and frequency.

The specific scGOS/lcFOS mixture may also have immunomodulatory properties similar to HMOS. In mouse models, dietary intervention with scGOS/lcFOS increased Th1 relative to Th2 parameters hence normalizing the Th1/Th2 immune balance, and reduced the allergic response to food allergens such as casein and whey,[19] and reduced airway hyper-responsiveness and other correlates of allergic asthma.[20] Adding scGOS/lcFOS to hydrolyzed infant formula appears to have a synergistic and long-lasting effect in protecting against allergic disease. In a prospective double-blind study, healthy infants at risk of atopy were randomized to either prebiotic-supplemented or placebo-supplemented hypoallergenic formula for a 6-month intervention period.[21] The prebiotic group had significantly lower incidence of atopic dermatitis (p =0.014).[21] Moreover, fewer collective episodes of infections (p =0.01); upper respiratory tract infection (p =0.07) or infections requiring antibiotics (p =0.10) were reported in the prebiotic arm versus placebo.[22] A prospective follow-up study at the age of 2 years found that infants from the prebiotic cohort had significantly lower incidences of adverse allergic reactions and cumulative incidence of atopic dermatitis, recurrent wheezing, and allergic urticaria (p <0.05) (Figure 1).[23] They also had fewer upper respiratory tract infections (p <0.01), episodes of fever (p <0.00001), and antibiotic prescriptions (p <0.05).[23] Preliminary data indicate that infants who received scGOS/lcFOS-supplemented hydrolyzate formula in the first 6

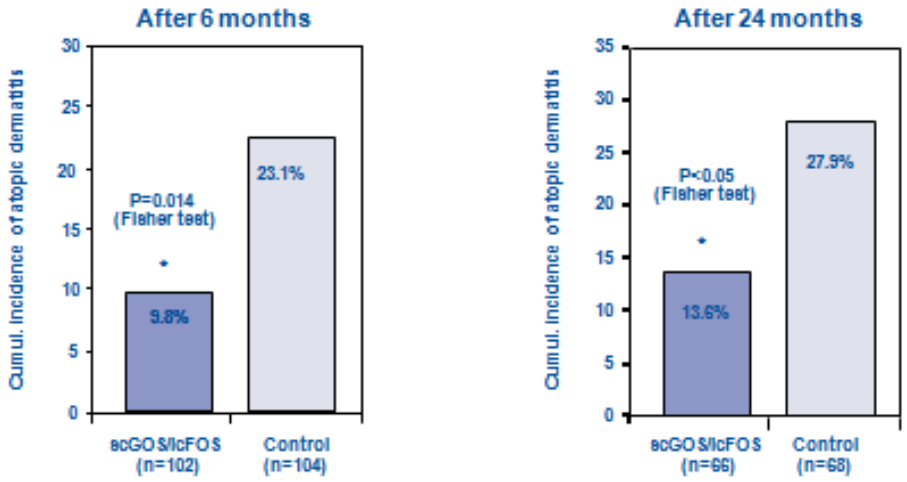

Figure 1. Prebiotic oligosaccharides protects formula-fed infants against atopic dermatitis during the 1st 6 months of life (A, left) up to age 2 years (B, right)

A. Reproduced from Archives of Disease in Chldhood, Moro G, Arslanoglu S, Stahl B, Wahn U, Boehm G, volume 91, 814-819, © 2006, with permission from BMJ Publishing Group Ltd. Source: B. J Nutr 2008;138:1091-1095.

months of life had significantly reduced allergic symptoms even at the age of 5.[24] Prebiotic oligosaccharides have also been shown to prevent atopic dermatitis in low-atopy-risk infants.[25]

Synbiotic mixture on atopic dermatitis

A new hypoallergenic infant formula (Danone) that combines eHF and synbiotic mixture (prebiotic scGOS/lcFOS and a probiotic bacteria *Bifidobacterium breve* M-16V), has been developed to further improve the intestinal microbiota and thereby help to prevent allergic diseases in formula-fed infants. In a randomized controlled trial, 90 exclusively formula-fed infants aged below 7 months and with confirmed moderate to severe atopic dermatitis, defined as SCORing Atopic Dermatitis (SCORAD) score of ≥15, were allocated to eHF with scGOS/lcFOS/*Bifidobacterium breve* M-16V or without synbiotic mixture for 12 weeks.[26] The primary outcome was atopic dermatitis severity on the SCORAD index; intestinal microbiota composition was a secondary outcome. After 12 weeks, both the synbiotic and placebo groups had significantly lower SCORAD scores than at baseline; however; there was no significant difference in SCORAD scores between the treatment arms. Among infants with IgE-mediated atopic dermatitis, SCORAD improvement at week 12 was significantly higher in the synbiotic group than in the placebo group (p =0.04).[26] The symbiotic group also had significantly greater percentages of *Bifidobacteria*, and lower percentages of *Clostridium lituseburense*/*Clostridium histolyticum* and *Eubacterium rectale*/*Clostridium coccoides*, as well as improved gut pH.

Atopic dermatitis placed the infants who participated in this study at high risk for developing asthma (the 'atopic march'). In a 1-year follow-up study to evaluate the impact of eHF with synbiotic mixture on respiratory symptoms and use of asthma medications,[27] the synbiotic group had reduced prevalence of 'frequent wheezing' and 'wheezing and/or noisy breathing apart from colds' than the placebo group. More children in the placebo group than in the synbiotic group required asthma medications. The new synbiotic mixture appeared to be beneficial for preventing asthma-like symptoms in the context of atopic dermatitis.

Based on these findings, a health-economics analysis to assess the use of scGOS/lcFOS for primary prevention of atopic dermatitis in the Netherlands, indicated that, compared with no prebiotics, prebiotic infant formula increases Quality-Adjusted Life Years (QALY) by 0.108 for an additional cost of €51, far below the threshold of €20,000/QALY; supplementation with scGOS/lcFOS is therefore a highly cost-effective way to prevent atopic dermatitis in the Netherlands, that may yield substantial cost savings at a national level when all clinical events are included.[28]

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