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Review Article

Human Milk Oligosaccharides as a Missing Piece in Combating Nutritional Issues during Exclusive Breastfeeding

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ABSTRACT

Extensive studies have shown that breast milk is the best source of nutrition for infants, especially during the first six months, because it fulfills almost all of their nutritional needs. Among the many functional building blocks in breast milk, human milk oligosaccharides (HMOs) have been receiving more attention recently. Furthermore, it is the third most common group of compounds in human milk, and studies have demonstrated the health benefits it provides for infants, including improved nutritional status. HMOs were previously known as the 'bifidus factor' due to their 'bifidogenic' or prebiotic effects, which enabled the nourishment of the gastrointestinal microbiota. Healthy gastrointestinal microbiota are intestinal health substrates that increase nutrient absorption and reduce the incidence of diarrhea. In addition, HMOs, directly and indirectly, protect infants against infections and strengthen their immune system, leading to a positive energy balance and promoting normal growth. Non-modifiable factors, such as genetics, and modifiable factors (e.g., maternal health, diet, nutritional status, environment) can influence the HMO profile. This review provides an overview of the current understanding of how HMOs can contribute to the prevention and treatment of nutritional issues during exclusive breastfeeding.

Keywords: Human milk; Oligosaccharides; Breast feeding; Nutritional status

INTRODUCTION

For infants up to six months of age, the best nutrition is exclusive breastfeeding. This practice is recommended by the World Health Organization (WHO) for up to one to two years [1]. Breastfeeding protects the infants against infections and malocclusion, increases intelligence, and reduces the risk of being overweight and diabetes [2]. According to the WHO, the overall rate of exclusive breastfeeding for infants under six months of age is only 40% [3].

Human breast milk contains macronutrients, micronutrients, digestive enzymes, hormones, immune cells, and many bioactive molecules. Human milk oligosaccharides (HMOs) are the third most abundant group of bioactive substrates in breast milk, following lactose (70 g/L) and lipids (40 g/L) [4]. This means that approximately 100 HMOs are fully characterized; therefore, it is assumed that more than 200 HMOs exist [5]. Oligosaccharides are only found in trace amounts in the mature milk of animals [6].

The quantity, quality, and balance in intestinal microbiota are essential to an infant's health and directly and indirectly affect nutritional status [7]. The disruption of the composition and function of the gut microbiome influence the nutritional status of infants, leading to undernutrition and obesity [8]. Wasting, stunting, and obesity in infants are associated with dysbiosis [9]. Originally, HMOs were identified as the 'bifidus factor' in breast milk with their 'bifidogenic' or prebiotic effects [4]. The presence of HMOs determines the development of the infant's gastrointestinal (GI) microbiota [10].

Genetic profile influences the HMO profile [4]; the α-1-2-fucosyltransferase (FUT-2) and α-1-3-4-fucosyltransferase (FUT-3) genes, in particular, specify the HMO profile. Furthermore, FUT-2 is responsible for the Se gene and categorizes mothers as secretors (Se+) or non-secretors (Se–), while the FUT-3 gene is responsible for the Lewis Group gene and categorizes mothers as Lewis+ or Lewis– [4]. Higher concentrations and more complex profiles of HMOs are found in Se+ Le+ mothers than in Se– Le– mothers [11]. The secretor status is influenced by geographic and racial differences, and almost 20% of the population is estimated to be composed of non-secretors [12].

This review explores how HMOs can contribute to the prevention and treatment of nutritional issues during exclusive breastfeeding.

HUMAN MILK OLIGOSACCHARIDES

The structure of HMOs consist of 3 to 14 monosaccharides [13]. Specifically, D-glucose (Glc), D-galactose, N-acetylglucosamine (GlcNAc), L-fucose, and sialic acid (Sia; N-acetyl neuraminic acid) are the five monosaccharide building blocks of HMOs [14]. There are three classifications of HMOs [7]; (a) 35-50% of the HMOs are neutral (fucosylated) HMOs (e.g., 2′FL, 3′FL, lacto-N-fucopentaose (LNFP) I, LNFP II, and LNFP III) and contain fucose at the terminal position; (b) 42-55% are nitrogen-containing neutral (non-fucosylated) and contain GlcNAc at the terminal position (e.g., lacto-N-neotetraose [LNnT] and lacto-N-tetraose [LNT]); and (c) the remaining 12-14% are acidic (sialylated; e.g., 3′SL and 6′SL) and contain Sia at the terminal position. The type, structure, and size of the HMOs are listed in **Table 1** [15].

The basic blueprints of HMO synthesis are generally applicable to all HMOs, although inter-and intra-personal alterations affect the variations [16]. These factors are further categorized into modifiable and non-modifiable factors. Genetic factors are non-modifiable factors determined by the FUT-2 and FUT-3 genes. The maternal secretor status has a more significant influence on HMO variations than does the Lewis blood type status, as described in **Table 2** [17,18]. However, only 60% of Asian mothers are secretors, compared to 74% of Caucasian mothers who are secretors [12]. The modifiable factors include maternal health and nutritional status, diet [19], duration of pregnancy [4], course of lactation [12], duration of breastfeeding [12], infant-related factors (e.g., sex, birth weight) [12], and the environment [11].

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Table 1. Highly abundant HMOs in human breast milk

Oligosaccharide (abbreviation)	Structure	Type and size
2′-fucosyllactose (2′-FL)	$Fuc\alpha_{1,2}Gal\beta_{1,4}Glc$	Fucosylated, neutral, triose
Lacto-*N*-fucopentaose I (LNFP I)	$Fuc\alpha_{1,2}Gal\beta_{1,3}GlcNAc\beta_{1,3}Gal\beta_{1,4}Glc$	Fucosylated, neutral, tetraose
Lacto-*N*-difucohexose I (LNDFH I)	$Fuc\alpha_{1,2}Gal\beta_{1,3}(Fuc\alpha_{1,4})GlcNAc\beta_{1,3}Gal\beta_{1,4}Glc$	Difucosylated, neutral, hexaose
Lacto-*N*-fucopentaose II (LNFP II)	$Gal\beta_{1,3}(Fuc\alpha_{1,4})GlcNAc\beta_{1,3}Gal\beta_{1,4}Glc$	Fucosylated, neutral, pentose
3′-fucosyllactose (3-FL)	$Gal\beta_{1,4}(Fuc\alpha_{1,3})Glc$	Fucosylated, neutral
Lactodifucotetraose (LDFT)	$Fuc\alpha_{1-2}Gal\beta_{1-4}(Fuc\alpha_{1-3})Glc$	Difucosylated, neutral, tetraose
Disialyllacto-*N*-tetraose (DSLNT)	$Neu5Ac\alpha_{2,3}$-$Gal\beta_{1,3}$-$(Neu5Ac\alpha_{2,6})$-$GlcNAc\beta_{1,3}$-$Gal\beta_{1,4}$-Glc	Difucosylated, acidic, hexaose
3′-sialyl lactose (3′-SL)	$NeuAc\alpha_{2,3}Gal\beta_{1,4}Glc$	Sialyl, acidic, triose
6′-sialyl lactose (6′-SL)	$NeuAc\alpha_{2,6}Gal\beta_{1,4}Glc$	Sialylated, acidic, triose
Monofucosylmonosialyllacto-*N*-hexaose (MFMSLNH)	$Neu5Ac\alpha_{2,6}$-$(Gal\beta_{1,3})$-$GlcNAc\beta_{1,3}$-$(Gal\beta_{1,4}$-$[Fuc\alpha_{1,3}$-$]GlcNAc\beta_{1,6}$-$)Gal\beta_{1,4}$-Glc	Sialylated and fucosylated, acidic, octaose
Lacto-*N*-tetraose (LNT)	$Gal\beta_{1,3}GlcNAc\beta_{1,3}Gal\beta_{1,4}Glc$	Nonfucosylated, neutral, tetraose
Lacto-*N*-neotetraose (LNnT)	$Gal\beta_{1,4}GlcNAc\beta_{1,3}Gal\beta_{1,4}Glc$	Nonfucosylated, neutral, tetraose

Glc: D-glucose, Gal: D-galactose, GlcNAc: N-acetylglucosamine, Fuc: L-fucose, Neu5Ac: N-acetyl neuraminic acid.
Adapted from Gastroenterology and Nutrition: Neonatology Questions and Controversies. 3rd ed. Philadelphia: Elsevier Saunders, 2019:43-58 [15].

Table 2. Milk oligosaccharide groups and the related genotypes

Milk group	Genotypes		Phenotypes		Fucosyl-Oligosaccharides*
	Secretor	Lewis	Secretor	Lewis	
1	Se/–	Le/–	Secretor	Lewis positive	2′-FL, LNDFH I+II, LNFP I+II+III, 3FL, LDFT, LNnT, LNT, LNH, MFLNH II
2	se/se	Le/–	Non-secretor	Lewis positive	LNDFH I+II, 3FL, LNFP II+III, LNnT, LNT, LNH, MFLNH II
3	Se/–	le/le	Secretor	Lewis negative	3FL, LNFP I+III, LDFT, 2′-FL, LNnT, LNT, LNH, MFLNH II
4	se/se	le/le	Non-secretor	Lewis negative	3FL, LNFP III, MFLNH II, LNnT, LNT, LNH

2′-FL: 2′-fucosyllactose, LNDFH: lacto-N-difucohexose, LNFP: lacto-N-fucopentaose, 3FL: 3′-fucosyllactose, LDFT: lactodifu-cotetraose, LNnT: lacto-N-neotetraose, LNT: lacto-N-tetraose, LNH: lacto-N-hexaose, MFLNH: monofucosyllacto-N-hexaose, DSLNT: disialyllacto-N-tetraose, LST: sialyllacto-N-tetraose, 3′SL: 3′-sialyl lactose, 6′SL: 6′-sialyl lactose.
*All sialyl-oligosaccharides, including DSLNT, LST, 3′SL, and 6′SL, are present in all milk groups.
Adapted from Bering (Nutrients 2018;10:1461) [18].

HMO biosynthesis is an extension of lactose biosynthesis, as all HMOs carry lactose at their reducing ends. This occurs in the Golgi apparatus of cells lining the alveoli and smaller ductules and begins with Glc [20]. Most of the effects of HMOs occur on cells in lymphoid tissues associated with mucous membranes because of the natural resistance of these cells to GI and duodenal digestion. These effects can also transit through the GI tract [21]. HMOs can also perform at the systemic level since approximately 1% of HMOs are absorbed and enter the systemic circulation [7].

ADVANTAGES OF HMOS

Maintenance of gut health

The proposed theories of how HMOs help combat malnutrition are based on the modulation of the gut microbiome [22]. The quantity and quality of the gut microbiome are related to malnutrition and obesity in infants [23]. The composition of the neonatal gut microbiota is known to be associated with HMOs [24]. The bifidogenic and prebiotic effects of HMOs promote the sustenance of the microbiome in infants [4].

Although the mechanisms are not clear, it is stipulated that the microbiome regulates the somatotropic axis, growth hormone, and insulin-like growth factor-1 activity to stimulate infant growth [23]. HMOs also influence appetite-regulating hormones, including ghrelin, glucagon-like peptide-1, and leptin [8]. Moreover, the microbiome influences metabolism and the nutritional status by affecting digestion, absorption, and energy storage [23].

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Abnormalities and immaturity of the microbiome disrupt the intestinal barrier, resulting in the deterioration and dullness of mucus, intestinal permeability, and immune dysfunction, affecting the health and growth of infants [23]. The essential amino acids, one of the vital nutrients for normal growth, are also influenced by microbiome dysbiosis [23]. Recent studies found that the normal composition pattern of the microbiota in the malnourished infants they examined was disrupted, suggesting that disrupted microbiota development impairs healthy postnatal growth [24].

Protection against infection

Infants are more vulnerable to infection by opportunistic pathogens because of their immature intestinal immune system [25]. To achieve good nutritional status, an infant must receive optimal energy intake; however, infections can negatively affect nutritional status. Frequent infection in infants causes deficits in calories, resulting in a negative energy balance, failure in weight gain, and eventually impaired linear growth [26].

The first line of defense against innate immunity is intestinal health and intestinal barrier function. Several mechanisms have been suggested for the anti-infection property of HMOs, mainly in that they (i) are believed to be the preferred substrate for the growth of certain "good" bacteria in the GI tract; (ii) prevent bacterial binding by acting as decoy molecules bound by pathogenic bacteria; and (iii) modulate the immune system through direct interaction [27].

Alkaline phosphatase is an important molecule for the maintenance of gut barrier function. The increased expression of alkaline phosphatase indicates the differentiation and growth of human intestinal epithelial cells, and alkaline phosphatase is known to be promoted by siallylactose [28]. Relatively high amounts of LNFP I and III and relatively low amounts of LNT are found in breast milk received by infants without sick days (e.g., diarrhea, fever, rash, coughing). The increased LNFP 1 levels are believed to help infants fight infection and maintain normal growth [29]. The incidence of diarrhea after two years is reduced by a relatively high abundance of fucosyl oligosaccharides. A high concentration of LNFP II in uninfected infants exposed to human immunodeficiency virus (HIV) results in a decrease in gastroenteritis and respiratory infections after 6 and 12 weeks, which also reduces the risk of HIV transmission and mortality [30].

Few studies have demonstrated the role of HMOs in respiratory viral infections. The viral load of the respiratory syncytial virus (RSV) has been shown to decrease in the presence of 2′FL, while the influenza viral load decreases due to the action of LNnT and 6′SL. Siallylated HMOs, 3-′SL, and 6-SL, can block the hemagglutinin of the influenza virus, thereby preventing influenza virus infection [31]. Subsequently, other additional Sia-containing HMOs have been identified to bind the influenza virus. The influenza viral load in airway epithelial cells has been shown to decrease in the presence of 6′SL and LNnT, while 2-FL influences RSV infection [32]. Infants have been found to experience mild respiratory and enteric problems by 6 and 12 weeks, which were observed to be associated with LNF II levels in breast milk and infant feces at two weeks postpartum [33]. The theory for this mechanism is still unknown. It is believed that absorbed HMOs enter the bloodstream and airways to protect infants against pathogens. Milk reflux coats the mucosal respiratory airways with oligosaccharides [34].

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Boosting of the immune system

The shifting of T cell responses to balanced Th1/Th2 cytokine production is the method used by HMOs to alter the immune response [35]. The Th17, Th22, and γδ T cells play an important role in the production of interleukin (IL)-22. This complex maintains the integrity of the epithelial barrier and regulates the composition of the microbiota [36]. The anti-inflammatory activity of 3′SL works by reducing the expression of IL-12 and IL-8 in Caco-2 cells while being mediated by nuclear factor kappa-light-chain-enhancer of activated B cells and stimulates the anti-inflammatory nuclear receptor peroxisome proliferator activated receptor gamma [37]. A study on *in vitro* inflammatory models showed the anti-inflammatory effects of neutral HMOs on the intestinal epithelium [38]. These effects were later studied in an infant receiving infant formula supplemented with 2′FL by measuring inflammatory cytokines in the infant's systemic circulation [39]. This study revealed lower levels of Tumour necrosis factor α, IL-1a, IL-1b, and IL-6 resembling 2′FL found in breastfed infants. Previous studies on LNFP III and LNnT also demonstrated their immunosuppressive effects [40], and LNFP III was found to induce IL-10 production in macrophages [41].

Infant growth

Infant growth is not related to the maternal secretor and Lewis group statuses [42]. However, the contents of HMOs that are influenced by the maternal secretor status (2′-FL and LNFP I) has been associated with infant growth and anthropometry. Specific HMOs found in secretor mothers, such as 2′-FL and LNFP I, have been associated with infant growth. This increases the consideration of supplementing infant formulas with 2′FL and LNnT as a part of infant nutrition [43].

A previous study found that the concentration of total HMOs in the colostrum was not particularly high and was associated more with the blood characteristics of the mother. High amounts of 1,2 fucosylated HMOs were found in secretor mothers, while only non-detectable or very low concentrations were found in non-secretor mothers [44]. These differences have biological consequences for infants. The incidence of diarrhea caused by the enterotoxigenic *Escherichia coli, Campylobacter jejuni*, or caliciviruses was significantly reduced in the presence of 1,2 fucosylated HMOs [45]. Furthermore, a low level of FUT-2 oligosaccharides reduced the diversity, richness, and abundance of Bifidobacterium. Although the secretory enzymes transferring 1,2-fucose were low, 1,3- and 1,4-fucosylated HMOs and the non-fucosylated residue were detected at high levels in the milk of non-secretor mothers [46]. Sprenger et al. [42] defined the level of 2′FL as a marker of secretor status correlated with a lower incidence of eczema and allergies mediated by immunoglobulin E.

In a group of Gambian infants, 3SL was positively correlated with the weight-for-age Z-score (WAZ). The higher production of 3′SL from 4 to 20 weeks was associated with a higher WAZ score of the infant at 20 weeks. In contrast, the same study showed a negative association between sialyllacto-N-neotetraose and WAZ scores [47].

A weight velocity at zero to five months of age and a fat mass index (FMI) at five months of age were positively associated with 2′-FL. Conversely, a negative association was found between height-for-age Z-scores (p=0.008), weight velocity at zero to five months of age (p=0.009), and FMI (p=0.033) with LNnT. In other words, a lower LNnT can lead to a high weight gain (HW group) (p=0.012). Certain HMOs, including 2′FL added to infant formula, are suspected to be the cause of excessive weight gain [48].

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Severely stunted infants at six months in the Malawian group previously received milk from mothers that produced significantly less sialylated HMOs than that of mothers with healthy infants. This showed a positive association between growth and sialylated HMOs. This finding was supported by another Malawian group that showed a significantly low level of total and sialylated HMO content in stunted infants [49]. At six months, each 1-mg/mL increase in disialyllacto-N-tetraose was associated with a 0.01 cm increase in the six-months length (β=0.01, p=0.04) [50].

In contrast, in a follow-up study of infants up to four months of age, there were no significant differences in body weight, body length, body mass index (BMI), and head circumference between infants receiving low or high FUT-2 associated HMOs. Although the data did not show a statistically significant result, male infants receiving milk with low 2′-FL were likely to have a slightly higher BMI at one month, though this was no longer observed after four months when they had a lower BMI and body weight gain [42].

CONCLUSION

HMOs play a crucial role in infants' nutritional status. Until recently, only a few studies carried out on humans have examined the association between HMOs and the nutritional status of infants, some of which possibly only had a small study population and limited study period. The results of these studies were also contradictory due to mixed interpretations. More data from large and longitudinal studies are needed to clarify the functions of HMOs.

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