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Role of Human Milk Oligosaccharides (HMOs) on Proper Growth, Immunity, and Tolerance in Ensuring Lifelong Health for Infants and Toddlers

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Abstract: Human milk oligosaccharides (HMOs) contain numerous biomolecules. It is the third most abundant solid component of breast milk, after lactose and lipids, that plays an important role in infant growth and the development of human life. Several studies have reported the health benefits of HMOs, which include modulation of the intestinal microbiota, anti-adhesive effect against pathogens, modulation of the intestinal epithelial cell response, development of the immune system, increasing the intestinal barrier and so many health benefits can be achieved through the presence of HMOs in breast milk. Infant growth is indirectly or directly dependent on so many compounds of the biological and chemical composition of mother milk, HMOs are one of them. The genetic background of the mothers and the diversity of HMOs are determined and the non-secretor mothers secrete lower HMOs than secretor mothers. The breastfed infants of secretor mothers gain more health benefits than those of non-secretor mothers. Here the study critically reviewed the role of HMOs in proper growth, immune system, and development in ensuring the health impact of infants and toddlers. The study also focuses on current knowledge of the HMOs study and the beneficial effect of HMOs types and their importance to infant growth and protection against NEC. HMOs are applied now in infant formulas to imitative nutrition composition of breast milk and their study and challenges are vastly discussed in a specific manner in the human study. In conclusion, it is stated that the supplementation of infant formula with 2′-FL and LNnT is a promising innovation for infant nutrition.

Keywords: Human Milk Oligosaccharides, Intestinal Barrier, Micro-Biota, Anti Bacteria, Necrotizing Enterocolitis, Pathogen Infection

1. Introduction

Nutrition in early childhood can play a major in human growth and development. Breastfeeding in early life can prevent all the infectious and non-communicable disease risks and protect humans during their childhood as well as their adulthood [1].

A healthy gut development helps in the process of growth in infancy. It contributes to growth and development by ensuring digestion and absorption of nutrients and fluids. The gut is also

key in the development of immunity insofar as it plays an important role as a barrier against infectious agents and it can interact directly with the immune system to systemic tolerance which can protect from allergies [2]. The World Health Organization (WHO) and the United Nations Children's Fund (UNICEF) mentioned the initiation of breastfeeding within the first hour of birth and advised exclusive breastfeeding for the first six months of life, without any other food or liquids, including water. The organizations further advised that breastfeeding should be continued for up to 2 years [3].

The breastfeeding composition is unique as it contains several substances including human milk oligosaccharides (HMOs) to help the infant's growth and development [4]. HMOs are non-digestible carbohydrates as they contain little nutritional value for the infant. HMOs are mentioned as the third-largest solid component in human milk [5]. These individual complex structures of human milk are virtually absent in cow milk and any other farmed animal milk. The most challenging for the pediatricians is to guarantee these advantages to newborns and infants who cannot get any benefit from breastfeeding but also to those breastfed infants whose mother's milk might lack some HMOs, which are currently approved in formulas [6].

There is much evidence that shows the actual benefit of HMOs on the process of infant growth and development. These biological molecules involve such long- and short-time benefits having many compounds such as carbohydrates, cells, cytokines, growth sectors, and immune globulins. Recently there have been made major advances in the inclusion of HMOs in infant formulas and some HMOs that are present in mother milk can be produced in engineered genetically microorganism for application in infant formulas [7].

In this review, we discuss the role of human milk oligosaccharides (HMOs) in infant growth and development, and then the review discusses the whole prospects and challenges of HMOs which essentially play an important role in infant growth and their lives.

2. Role of Human Milk Oligosaccharides (HMOs)

The immune system in the early stages is immature and its rapid growth mainly depends on the bioactive molecules of breast milk and also encounters the new microbiota and new dietary components in the early stages of the life cycle [8]. One of the most important bioactive molecules is human milk oligosaccharides which play an important role in human growth. HMOs are unique and cannot be found in the same variety and these are not found in any other composition in other mammals [9]. The concentration of HMOs ranges from 20-25 g/l in colostrum and 5-20 g/l present in mother milk which makes them the third-largest solid component in human milk and makes them unique of all the biological molecules. There are so many benefits of HMOs which are responsible for human growth and development.

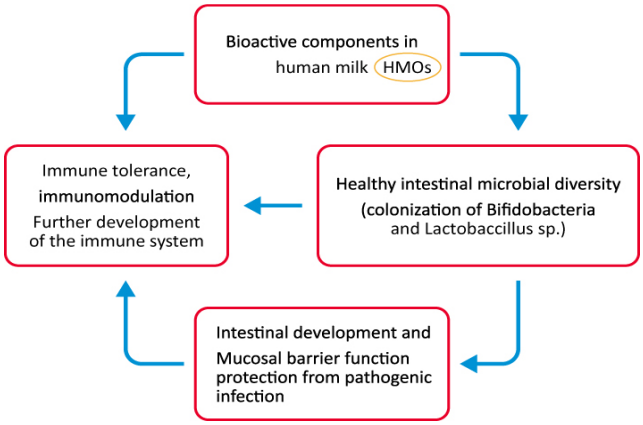

Figure 1. *Role of Human Milk Oligosaccharides (HMOs).*

2.1. Role of HMOs in Microbiota

HMOs have a strong impact on the colonization of the intestine by bacteria which plays a major role and is also essential for human health [10]. In the early stages of life, it is critical for the development of the intestinal microbiome and infant diet is an important factor for the proper growth of a microbiome. HMOs, play a role to resist gastric acidity and the range of HMOs can reach both small and large intestines to modulate the whole process and composition of the resident microbiota.

2.2. HOMs Support the Beneficial Bacteria

HMOs, support the beneficial bacteria in many ways especially Bifidobacterium species which is known as a dominant species in breastfed infants [11]. Not every Bifidobacterium species can consume HMOs but one of the species can consume HMOs from human milk as the source of carbohydrate. All the beneficial bacteria can degrade HMOs by using intracellular and extracellular glycoside hydroleses. The extracellular HMOs degradation of B. bifidum results in the production of sugars and thereby stimulates the growth of other species that can utilize these carbohydrates as a source of energy [12]. HMOs are also useful in enhancing the binding of commensal bacteria to epithelial cells and also support the colonization of microbiota in infants. The influence of HMOs is great that it can modulate the growth and fermentation of other beneficial bacteria and E. hallii consumes acetate, lactate, and 1,2-propanediol, which are the HMOs fermentation products of bifidobacteria, and subsequently produces the SCFAs butyrate and propionate, thereby supporting gut barrier function and the immune system [13].

2.3. Reduce Pathogen Infection

HMOs can prevent many pathogen infections in several ways by serving soluble decoy receptors or by inhibiting the growth of pathogens. Many pathogens need to attach to the glycocalyx layer, HMOs can bind HMOs to pathogens and serve as antiadhesive antimicrobials, and prevent microbial infection by the structural resemblance of the glycocalyx layer [14]. Recent studies showed that HMOs isolated from

human milk significantly inhibited the growth of GBS by up to 89% and biofilm formation by up to 90%. Also, the studies showed the HMOs isolated from human milk possessed significant antimicrobial activity against Acinetobacter baumannii up to 11% and could up to inhibit biofilm formation up to 60% [15].

2.4. Protection Against Necrotizing Enterocolitis

Necrotizing Enterocolitis (NEC) is a life-threatening gastrointestinal condition that mainly occurs in preterm newborns with very low birth weight. It can be harmful to the newborn baby and can be devastating for the preterm newborn. HMOs act as protective factors against microbial dysbiosis, and intestinal and immune system immaturity, which are recognized as the main etiological factors behind NEC [16]. The presence of a high level of HMOs shows active regulation to all the processes of these compounds which adapt immunological needs of infants as well to their nutritional necessities. Recent interesting findings suggest that HMOs may prevent injury of the intestinal mucosa by modulating the expression of TLR4 on epithelial cells. Moreover, HMOs exact their role as proactive factors and protect infant growth against NEC.

1) Prebiotics, supporting a favorable microbiome to prevent pathogen growth, contribute to the integrity of the intestinal mucosa.
2) They act as antimicrobials, preventing pathogen adhesion to epithelial cells.
3) At last, they modulate the immune response, thus limiting the magnified inflammation occurring during NEC.

2.5. HMOs Increase Intestinal Barrier Function

The primary function of the gastrointestinal tract is to digest and absorb nutrients, HMOs act as proactive factors and enhance the intestinal barrier function to protect the function. HMOs, support intestinal barrier function both through indirectly influencing microbiota composition and directly by modulating intestinal cells. HMOs can support intestinal barrier function by promoting the growth and supporting the production of fermentation products by Bifidobacterium species. A study found in vitro that B. infants ATCC15697 grown on mixtures of HMOs isolated from mother milk had a significantly higher capacity to adhere to HT-29 cells, which induced higher expression of tight junction proteins such as occluding and junction adhesion molecule (JAM-A) in gut epithelial cells [17]. Literature also described HMO isolated from human milk can increase the intestinal cells both in vitro in vivo and ex vivo. The study further showed that HMO can increase the level of MUC2 protein and can decrease the permeability of the intestine to macromolecular dextran. The study also described HMO can induce MUC2 gene expression and decrease the permeability of dextran during enterohemorrhagic Escherichia coli O157:H7 challenge of intestine cells [18].

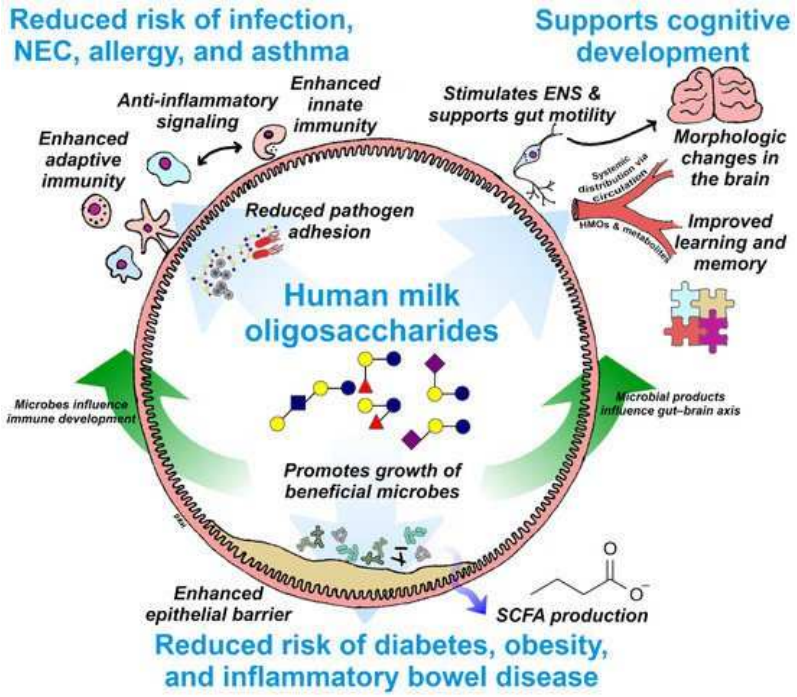

Figure 2. *Benefits of Human Milk Oligosaccharides (HMOs).*

2.6. Presence of HMOs in Infant Formula

According to World Health Organization (WHO), six months of breastfeeding is just after birth. But for a variety of reasons, it cannot possible to continue breastfeeding, and then it continues with alternative cow milk. These infants receive cow milk-derived infant formulas, which attempt to mimic the nutritional composition of breast milk as closely as

possible [15]. There are non-digestible fibers such as galactooligosaccharides (GOS) and inulin-type fructans that are often added to the commercial infant formulae which are available as substitutes for some of the HMOs' beneficial effects [19]. HMO is known as carbohydrates that are safe for a long time because the biological and chemical processes are produced to synthesize HMO and making it essential to evaluate the safety of the production procedure [20]. he Panel concluded that LNnT and 20 -FL is considered safe as food supplements for 1-3-year-old toddlers. Intake of these HMOs may not exceed 0.6 g of LNnT and 1.2 g of 20 -FL (alone or in combination) per day. For 4-18 years old children, 1.5 g of LNnT and 3 g of 20 -FL (alone or in combination) per day are recommended [21]. A study concluded that the USA's Food and Drug Administration (FDA) considers three HMOs to be Generally Regarded as Safe (GRAS). These HMOs are 20 -FL (GRAS notice no 546/571/650/735), and (GRAS notice no 659), as well as 30 -SL (GRAS notice no 766) [22]. A study conducted in vitro and in vivo safety assessment experiments of genetically modified E. coli K12 strain produced 3-FL and concluded that 3-FL is safe as a nutritional ingredient in foods [23].

Table 1. *The three HMOs are approved for use in infant formula, with dates of approval by the European Food Safety Authority and the US Food and Drug Administration.*

HMOs	Approval in EU (European Food Safety Authority	Approval in the USA (US Food and Drug Administration)
2 -Fucosyllactose (2 -FL)	2015	2016
Lacto-N-neotetraose (LNnT)	2015	2016
3-Sialyllactose (3′-SL)		2019

The capacity of HMOs to modulate the immune function and reinforce the gut barrier might support their ability to afford health paybacks in adults, rather than in infants only [24]. The focus on HMOs supplementation in the infants, as well as the transfer of HMOs to the adults, seems to rise and commercialization slowly but it will happen and make a case about HMOs adult supplementation.

2.7. HMOs and Effect of Immunomodulatory

The immune system of an infant is functionally is not strong enough and HMOs play a major role in developing the systematic immune system of an infant. HMOs can bind to cell surface receptors expressed on epithelial and immune system cells, and thereby modulate neonatal immunity in the infant gut [25]. As an example, HMOs can influence the expression of multiple cytokines and chemokines, adhesion molecules, and receptors. The results of this expression and effects can show that HMOs have a necessary contribution to building the maturation of intestinal immune response. In terms of the effect on immune cells, HMOs isolated from pooled human milk, induced semi-maturation of human monocyte-derived dendritic cells, and elevated levels of IL10, IL-27, and IL-6 but not IL-12p7 and TNF-α, thereby playing a modulatory role in the development of the neonatal immune system [26]. Research conducted that 2 -FL, abundantly available in human milk, enhanced Th1-type IFNγ and regulatory IL-1 secretion of peripheral blood mononuclear cells. Dendritic cells exposed to 20 -FL instructed the secretion of IFNγ and IL-1 from CD4+ T-cells, suggesting the growth of a regulatory Th1 response [27]. Around 1% of HMOs can reach the systematic circulation, HMOs not only impact the intestinal fact but also influence the development of many other organs [28]. A study described those mixtures of HMOs isolated from pooled human milk significantly reduced uropathogenic Escherichia coli (UPEC) internalization in bladder epithelial cells and it attenuated the cytotoxic and pro-inflammatory effects induced by UPEC as well [29]. Some HMOs contain β1-3- or β1-4-linked galactose at the non-reducing end, which can be the potential target for galectin-mediated interactions. The binding affinities of 31 free HMOs with the galectins Gal-1, Gal3, and Gal-7 were studied by catch-and-release electrospray ionization mass spectrometry (CaR-ESI-MS) [30]. In such studies and analyses, HMOs showed a large high binding affinity to galectins, and galectins are known as potential HMOs receptors s for immune system mediation [31].

3. Conclusion and Further Considerations

The importance of HMO and its beneficial effects on infants are huge as they are essential in developing the immune system, protecting against NEC, intestinal barriers and so many. But there are so many limitations present in the human study of HMOs. HMO is a vast area to discuss but there is only a limited part to discuss in human study and scientists are still trying to discuss the particular section present in HMOs study. The efforts of scientist should be more encouraged as we know HMOs has a vast human health beneficial effect and if there will be more research its beneficial effect will come in the present study. The health benefit is specific for specific HMO types so the effort of gaining more research about this sector needs more encouragement with confirmed bioactivities that can be applied to the infant formulas. Another change needs to be done in the HMOs study to understand its beneficial effect more than the impact of an individual and well-defined mixture of HMOs in intestine cells in a structure-dependent manner. This proposal should be done immediately as it can protect premature babies from the risk of NEC. The first 8 weeks' infants do not have the full enzymatic ability to ferment all HMOs and blood group deficiencies are also can be found so more insight into HMOs study can provide the information and solution for blood groups and microbiota in different age classes. Metabolism was able to differentiate the

phenotypes related to specific patterns of HMOs and it helped the investigators the genotype is not the only factor that can determine the production of HMOs. In fact, the production of HMOs depends on many unidentifiable or identifiable factors such as geographical location, ethnicity, maternal diet, and season. It can be hypothesized that HMOs study can further be improved in a more specific manner and can achieve specific formula and supplemental infant formula, can guarantee the optimal nutrition regime of a newborn. The new supplemental formula can be useful for exploring future HMOs functions and types.

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