American Journal of Pediatrics
2024; 9(4): 204-209
http://www.sciencepublishinggroup.com/j/ajp
doi: 10.11648/j.ajp.20230904.13
ISSN: 2472-0887 (Print); ISSN: 2472-0909 (Online)

Review Article

Human Milk Oligosaccharides and Development of Gut Microbiota with Immune System in Newborn Infants

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To cite this article:

Sanat Kumar Barua, Jagadish Chandra Das, Mohammad Maruf-UL-Quader, Zabeen Chowdhury, Salina Haque, Muhammad Jabed Bin Amin Chowdhury, Aparup Kanti Das, Dhiman Chowdhury. Human Milk Oligosaccharides and Development of Gut Microbiota with Immune System in Newborn Infants. *American Journal of Pediatrics*. Vol. 9, No. 4, 2024, pp.204-209. doi: 10.11648/j.ajp.20230904.13

Received: September 11, 2023; **Accepted**: September 28, 2023; **Published**: October 14, 2023

Abstract: Human milk oligosaccharides (HMOs) constitute a significant and intriguing component of human milk, ranking as the third most abundant solid constituent following lactose and lipids. Meanwhile, gut microbiota encompasses an array of microorganisms, spanning bacteria, archaea, fungi, and viruses, residing within the digestive tract. The intricate interplay among human milk oligosaccharides (HMOs), gut microbiota, and the immune system holds substantial implications for the initial developmental stages of newborns. This comprehensive review aimed to delve into the multifaceted role of HMOs in molding gut microbiota and their profound contribution to the maturation of the immune system in neonates. By conducting a meticulous systematic review of pertinent literature, this study explored the intricate interrelationships among HMOs, gut microbiota, and the immune system in newborn infants. The review analyzed a substantial corpus of recently published original research articles and comprehensive review papers. Google Scholar, PubMed, and SCOPUS served as robust and dependable sources for data acquisition. Besides these, some other reliable sources were also used. Through this article, readers will acquire a lucid comprehension of HMOs' pivotal role in shaping gut microbiota dynamics and fostering immune system maturation in neonates. The insights garnered from these interactions hold the promise of steering interventions geared toward optimizing neonatal health outcomes. Nonetheless, further research is imperative to unveil specific underlying mechanisms and potential therapeutic avenues.

Keywords: Human Milk, Oligosaccharides, HMOs, Neonatal Immunity, Gut Microbiota, Digestive Tract

1. Introduction

Human milk stands out as the ultimate source of nourishment for newborn infants, acknowledged for not only supplying crucial nutrients but also containing bioactive elements that foster their growth and development [1]. Among the various bioactive components nestled within breast milk, Human Milk Oligosaccharides (HMOs) hold particular significance due to their immunological effects and potential to influence the development of the gut microbiota and immune system in neonates. HMOs are intricate carbohydrates exclusive to human milk, possessing structural diversity and functional attributes that set them apart from other dietary carbohydrates [2]. Remarkably, they rank as the third most prevalent solid component in human milk, following lactose and fat [2, 3]. Interestingly, infants do not digest HMOs; instead, these complex carbohydrates serve as sustenance for the burgeoning gut microbiota. Research has demonstrated that HMOs act as prebiotics, selectively fostering the growth of beneficial bacteria such as Bifidobacterium and Lactobacilli while impeding the proliferation of potentially harmful pathogens [3, 4]. This

selective effect is thought to contribute to the establishment of a healthy gut microbiota in early life, which is essential for the development of the immune system and overall health [5-7]. HMOs have been found to exert direct immunomodulatory effects on infants, enhancing the maturation and function of immune cells. Notably, dendritic cells and B cells are influenced, leading to the production of specific antibodies and influencing immune responses. Additionally, HMOs possess antimicrobial properties, directly neutralizing pathogens in the infant's gastrointestinal system. The intricate interplay between HMOs, the gut microbiota, and the immune system is delicately balanced, and any disruption in this equilibrium is associated with an increased risk of immune disorders, notably allergies, asthma, and autoimmune diseases [8-11]. The development of innovative nutritional strategies, including HMO-based supplements or fortifiers for infants who are not exclusively breastfed, is of paramount importance [12-15]. A comprehensive understanding of these vital oligosaccharides in infants' immune systems is crucial. Regrettably, there is a lack of clear understanding among many in the field about HMOs and their role in the development of the gut microbiota and the immune system in neonates. It is hoped that this review will serve as a valuable resource for newcomers in the fields of Biotechnology and Pediatric Medicine, orienting them toward the development of innovative treatment strategies in this significant area of research.

2. Methodology

A systematic search on several randomized controlled clinical trials, meta-analyses, and systematic reviews, was conducted to get a clear concept of the role of HMOs in molding gut microbiota and their profound contribution to the maturation of the immune system in neonates. As per the inclusion criteria of this study, randomized controlled clinical trials, meta-analyses and systematic reviews were included.

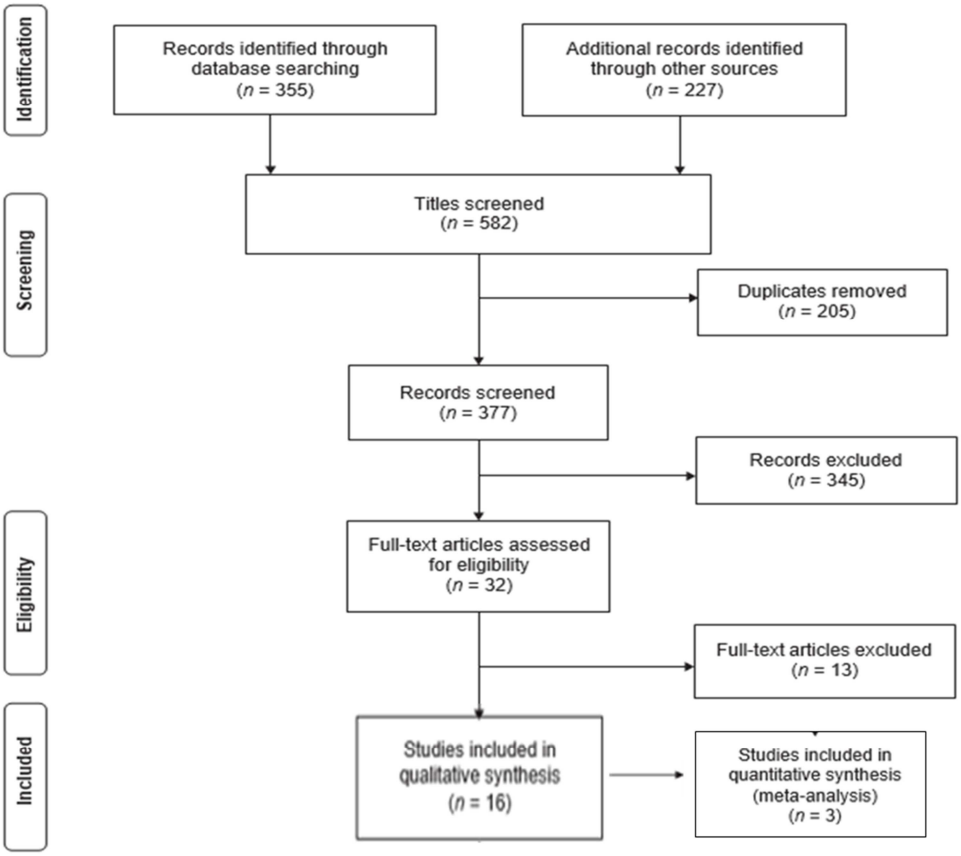

Figure 1. *PRISMA flow chart.*

From database screening as well as other sources in total 582 articles were selected primarily. After duplicate (n=205) removal, 377 articles were found. After records exclusion, only 32 articles were selected. Finally, after full-text article exclusion, only 19 articles were confirmed among which 16 were defined for basic qualitative information and the rest 3 were defined for basic quantitative information. Besides those 19 articles for more clarification of basic information, many references were collected from some additional similar articles. Analysis and determination of the quality of the studies were based on a questionnaire from SBU (the Swedish Council on Health Technology Assessment) [15].

2.1. Human Milk Oligosaccharides

Despite being indigestible to newborns, human milk oligosaccharides (HMOs) have attracted great interest due to

their abundance (1-2% w/v) and structural diversity non breast milk [16]. Technologies that provide sensitivity, repeatability, high throughput, and quick identification of particular structural isomers within complicated biological materials are essential for the efficient study of milk glycans. HMO measurement has historically been accomplished utilizing a variety of separation techniques, including various kinds of capillary electrophoresis and high-performance liquid chromatography (HPLC), both of which make use of standard substances [16]. To separate oligosaccharide isomers, liquid chromatographic (LC) methods such hydrophilic interaction LC, reverse phase (C18), and porous graphitized carbon have been used [17]. In HMO analysis, porous graphitized carbon has proven to be the most efficient approach for isomer separation [17, 18]. The lack of commercially accessible HMO standards, which is further exacerbated by the difficulty of clarifying HMO structures, restricts the application of LC procedures. Since it needs large quantities of pure compounds, nuclear magnetic resonance (NMR) has historically been the main technique for elucidating structures in less common species [19]. A sensitive technique of LC detection and structural elucidation capabilities are provided by mass spectrometry (MS) (58). While HMO composition identifies the sugar residues present without linkage information, structural elucidation of the structure of HMOs exposes the links between sugar residues within them. Tandem MS approaches are able to discriminate between stereoisomers such glucose (Glc) versus galactose (Gal) versus mannose, however they rely on well-known standard structural properties and only offer structural insights [20]. A combination of MS, tandem MS, and exoglycosidase digestion is used to efficiently clarify HMO structures. Using this method, 75 HMO structural isomers have been identified and annotated, totaling over 200 entire milk structures from different animal species. It is noteworthy that only 50 structures account for 99% of the abundance in human milk, highlighting the effectiveness of this approach [3]. For nutritional phenotyping in health and disease investigations, quantifying HMO structures in complicated mixes like biofluids is essential. Quantitative data for fold change comparisons between sample groups is provided by relative abundances. Comparison of peak regions to established standards can lead to absolute quantitation. Ion count, chromophoric tags like anthranilic acid or 2-aminobenzamide, deuterium labeling, and nano-LC/MS are only a few of the several LC/MS quantification techniques employed. For certain applications, triple quadrupole MS is also gaining popularity for multiple reaction monitoring, especially in the study of bovine milk oligosaccharides [21]. When compared to the quantity and complexity of the soluble oligosaccharides present in the milk of any other mammal, human milk is unmatched [22]. From 7 g/L in mature breast milk to 23 g/L in colostrum, the average HMO concentration varies [23]. The functional effects of this structural variation are a major area of study interest. HMOs are complex soluble sugars made up of different mixtures of the monosaccharides glucose (Glc), galactose (Gal), N-acetylglucosamine (GlcNAc), fucose (Fuc), or sialic acid (Neu5Ac). The creation of a lactose core, which is mediated by -galactosyltransferase in the presence of -lactalbumin, is the first step in the production of HMOs in the mammary gland. This lactose core is shared by almost all HMO structures [24].

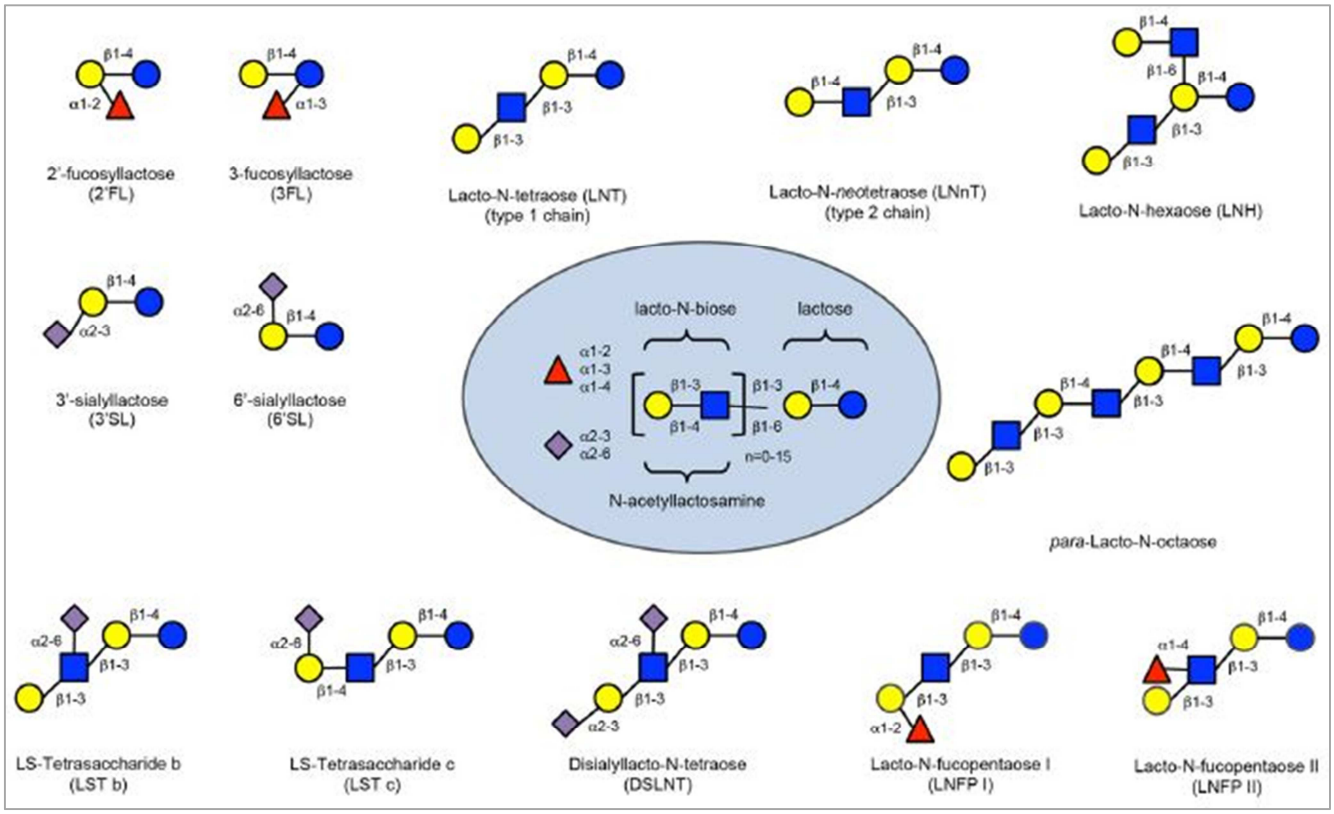

Figure 2. *Human milk oligosaccharide composition blueprint. [11].*

Enzymatic elongation of lactose can occur by 1-3 linkage to produce lacto-N-biose or 1-6 linkage to produce N-acetyllactosamine. By including lacto-N-biose and N-acetyllactosamine units with 1-3 and 1-6 links, attaching Fuc with 1-2, 1-3, or 1-4 linkages, and/or including sialic acid residues with 2-3 or 2-6 linkages at terminal locations, the fundamental structure of HMOs can be further expanded. Neutral HMOs make up 35–50% of breast milk, 12–14% of sialylated HMOs, and 42–55% of nonfucosylated HMOs, according to a recent research [25].

2.2. HMOs Essential for Newborn Gut, Immune Development

HMOs have a variety of functions, including as controlling the microbiota, defending against pathogens, and modifying epithelial cells [26]. They have a considerable impact on bacterial colonization in the newborn intestine, which is particularly important because the first year of life sees the colonization of the infant gut by about 1014 bacteria. The microbiome's growth at this time depends heavily on the infant's nutrition. HMOs may enter both the small and large intestines, where they function as substrates for resident microorganisms and affect the makeup and activity of the gastrointestinal microbiota. HMOs are indigestible non the upper gastrointestinal tract because they lack the essential enzymes and transporters. Notably, HMOs encourage the development of advantageous microbes like Bifidobacterium, which frequently makes up a sizeable fraction of the bacterial community in breastfed infants' feces [27, 28]. Using transporters, glycoside hydrolases (GHs), and carbohydrate-binding proteins, these bacteria break down HMOs, according to genomic research of certain infant-derived Bifidobacterial strains [29]. Specifically, B. breve, B. bifidum, B. longum, and B. babies exhibit HMO-degrading enzyme expression [30, 31]. Additionally, the fact that sialidases and fucosidases are present in both Bifidobacterium and Lactobacilli and allow them to break sialic acid (Sia) and fucose (Fuc) suggests a coevolutionary connection with HMOs [32]. Additionally, Bifidobacterium affects the makeup of other microbes. For instance, B. bifidum has the ability to release GHs to break down HMOs extracellularly, liberating digested sugars that other bacteria can use to create SCFAs like butyrate and propionate. Due to their interactions with host epithelial cells that promote mucin secretion, boost blood flow to the mucosa, and control immunity, these SCFAs are essential for intestinal health [33, 34]. Common adult gut microbiota member E. hallii is unable to use fucose (Fuc) for growth. However, it may use 1,2-propanediol (1,2-PD), a byproduct of B. infantis produced by the breakdown of Fuc, when cocultured with B. infantis. This indicates that E. hallii and B. infantis have a trophic relationship [35]. G protein-coupled receptors (GPCRs) have been demonstrated to be activated by HMOs, which has an impact on a variety of physiological processes, including development, taste, olfaction, heart rate control, hormone signaling, and neurotransmission. Two mechanisms contribute to this activation: enhanced microbiota synthesis of kynurenic acid (KYNA), which in turn activates GPR35 [36, 37], and direct activation by 6′-SL and LNT. To begin host invasion and spread illness, many pathogens, including bacteria, viruses, fungi, and protozoan parasites, often need to attach to the glycocalyx (the carbohydrate-rich layer covering epithelial cells). However, by acting as soluble decoy receptors, HMOs can prevent infection [27]. They bind to pathogens and stop them from adhering to epithelial cell surface receptors, letting the pathogens to go through the digestive system without causing any harm. For instance, 2'-FL severely impairs Campylobacter jejuni, a frequent cause of potentially fatal newborn diarrhea, and reduces its colonization by 80%. Recent research suggests that 2'-FL directly suppresses lipopolysaccharide-mediated inflammation during enterotoxigenic Escherichia coli (ETEC) invasion of intestinal epithelial cells. HMOs are involved in immunity and the urinary system. Similar to this, 15 mg/mL HMOs prevent uropathogenic Escherichia coli (UPEC) from adhering to epithelial cell monolayers by delaying the p38 MAPK and p65 NF-B signaling pathways [8, 38]. HMOs dramatically increase infants' resistance to the potentially fatal gastrointestinal infections rotavirus and norovirus. Mechanical study suggests that HMOs protect the body from viral infections by mimicking receptor sites, preventing viruses from invading host cells. Additionally, they reduce virulence by enhancing immunity by producing IL-10 and -interferon. The rotaviruses G1P [39] and G2P [40] have recently been demonstrated to be considerably resistant to the antiviral actions of 2'-FL, 3'-SL, and 6'-SL. Particularly, 2'-FL prevents G1P [39] rotavirus infection, whereas a mixture of 3'-SL and 6'-SL effectively prevents G2P [40] rotavirus infection. It's crucial to remember that not all rotavirus infections may be prevented by HMOs, as is the case with newborn rotavirus G10P [41], whose infectiousness rises with the concentration of LNT and LNnT. HMOs can prevent norovirus infections by acting as antiviral medicines. Histo-blood group antigens (HBGAs), which are present in a variety of mucosal epithelia and as free oligosaccharide fluids in the physiological system, act as crucial binding sites for norovirus adherence. High-mass HMOs with plenty of -fucose, which resemble HBGAs in structure, can bind to norovirus and prevent infection in breastfed children [42, 43]. HMOs are important in avoiding infections brought on by protozoan parasites in addition to thwarting bacterial and viral invaders. [26] HMOs, for instance, make it harder for Entamoeba histolytica, an anaerobic amoebozoan that causes over 55,000 fatalities yearly throughout the world. It was shown in an in vitro experiment that LNT, which has the terminal Gal structure, functions as a soluble decoy receptor, preventing Entamoeba histolytica from adhering to intestinal epithelial HT-29 cells. [26] Particularly in the early stages of pregnancy, intestinal fungal infections can significantly endanger the health of a newborn. For instance, systemic candidiasis has a death rate of around 20% and an invasion rate of roughly 10% in neonates. The Candida albicans hyphal-specific adhesion

protein is encoded by the gene ALS3, which has been demonstrated to be downregulated by HMOs in recent studies. As a result, C. albicans and epithelial cells adhere to one another less readily in the first stages of infection. HMOs also prevent C. albicans from attaching to certain spots on its surface, preventing it from interacting with intestinal epithelial cells [44, 45].

3. Conclusion

In conclusion, the role of human milk oligosaccharides (HMOs) in shaping the gut microbiota and immune system development in newborns is paramount. HMOs, abundant in human breast milk, not only serve as nourishment for beneficial gut bacteria but also act as soluble decoy receptors against a range of pathogens, including bacteria, viruses, fungi, and protozoan parasites. They play a multifaceted role in enhancing infant immunity, preventing infections, and influencing vital physiological functions. This intricate interplay between HMOs, the gut microbiota, and the immune system underscores their critical role in safeguarding newborn health. Understanding the mechanisms and functions of HMOs is pivotal for developing innovative nutritional strategies and treatments for infants, further emphasizing the importance of breastfeeding in early life.

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