An Introduction to the Basic Science and Complexity of Human Milk Oligosaccharides

Human milk oligosaccharides (HMOs) are complex sugars (carbohydrates) that represent the third most abundant component of human milk after lactose and lipids. More than 150 different and structurally distinct HMOs have been identified so far and accumulating evidence indicates strong structure-function relationships — in other words: different HMOs have different functions. HMO composition varies tremendously between different women and to a lesser extent over the course of lactation. Recent research focuses on how fixed and modifiable maternal factors influence HMO variation. So far, maternal genetics appear to be the strongest predictor of HMO composition. Single nucleotide polymorphisms (SNPs) in genes that encode specific glycosylation enzymes involved in HMO biosynthesis can alter HMO composition to an extent that entire groups of HMOs are missing from the milk. Other maternal factors have more subtle effects on HMO composition, increasing or decreasing the absolute concentration and/or relative abundance of individual HMOs on a continuous scale. While it is important to understand which maternal factors drive the variation in HMO composition and how, most research focuses on whether and how HMOs impact infant health and development. Once ingested, HMOs resist degradation and reach the distal parts of the gastrointestinal tract. HMOs serve as natural prebiotics and help shape the infant gut microbiome with immediate and potential long-term consequences for health and development, including infant growth, body composition and potential risk of childhood obesity. However, HMOs are more than just “food for bugs”. HMOs serve as antimicrobials and antiadhesives that keep potential pathogens in check. HMOs also have direct effects on epithelial cells as well as on immune cells, both locally in the gastrointestinal tract as well as systemically. Some of the effects of HMOs are highly structure-specific and dose-dependent, suggesting that they interact with specific host and/or microbial receptors. Specific HMOs are required to exert these effects while other, structurally distinct HMOs cannot mimic these effects. Other HMO effects require a specific “mixture” of HMOs with specific ratios of different HMOs to each other. One HMO alone is ineffective; instead a group of different HMOs is required to act together in modulating the composition and activity of microbial communities and/or a complex immune system response. HMOs were first discovered in the mid 1950s and HMO research has come a long way since and has been greatly accelerated over the past few years due to advances in analytical technologies as well as in methods to generate individual HMOs at large scale for research and application. However, we are still at the very beginning of uncovering the complexity of HMOs and understanding the full potential of how HMOs influence the immediate and long-term health and development of infants and mothers.
A number of benefits of breastfeeding, particularly protection against child infections, may be, at least partially, related to the presence of human milk oligosaccharides (HMOs). Among others, the postulated effects of HMOs include prebiotic and antiadhesive/antimicrobial effects, modulation of intestinal epithelial cells, and immune modulation. Progress in biotechnology nowadays allows the production of at least some HMOs. Two HMOs, 2-fucosyllactose (2’-FL) and lacto-N-neo-tetraose (LNnT), have recently been added to infant formula, either alone or in combination. We are at the beginning of a new era in infant nutrition which poses a number of clinical questions, the answers to which should be evidence-based.

Evidence-based medicine (EBM) relies on finding and critically appraising the relevant scientific literature with regard to the trustworthiness of the data reported and with the purpose of determining the merits of an intervention. This knowledge is then implemented in clinical care. The key elements of practicing EBM are formulation of an answerable question, finding the evidence, critical appraisal of the evidence, and applying the evidence. The extent to which one can draw conclusions from published clinical research depends on whether the data and results of the study are free of biases. If there are biases, the task is to consider how they might affect the results.

In the context of EBM, potential benefits, along with safety, should be considered when adding a new ingredient, such as an HMO, to formulas. Major databases were searched up to January 2019 for randomized controlled trials to review current evidence on HMO-supplemented formulas. The administration of currently evaluated HMO-supplemented formulas to healthy infants does not raise safety concerns with regard to growth and adverse effects. Some favorable clinical effects are possible; however, further high-quality randomized clinical trials are needed. These trials should assess outcomes over a longer period of time and use validated outcomes that are agreed on by experts in the field of infant nutrition. Future research should also examine the optimal composition and dosage for HMO interventions and consider effectiveness in different settings/populations. Stay tuned for future publications.
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