Human Milk Oligosaccharides and the Preterm Infant

A Journey in Sickness and in Health

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KEYWORDS

• Human milk oligosaccharides • Glycans • Preterm infant • Nutrition • Microbiome • Immune system

KEY POINTS

- Human milk oligosaccharides (HMOs) are the third most abundant component of human milk.
- Preterm infants consume several grams of approximately 200 structurally diverse HMOs daily from mother's own or donor milk. Formula-fed infants and infants on parenteral nutrition do not currently receive any HMOs.
- HMOs are proposed to support infant health, growth, and development by acting as prebiotics, antimicrobials, antiadhesives, and modulators of cell responses.
- Preclinical and cohort studies suggest HMOs are protective against necrotizing enterocolitis (NEC) in preterm infants.
- Larger mother-infant cohort and human intervention studies are limited, but recent technological advances in both HMO analysis and HMO synthesis help overcome hurdles and challenges.

INTRODUCTION

Preterm infants are a diverse group of babies with varying nutritional and medical needs, depending on the level of physiologic maturity at birth, birth weight, and neonatal morbidity, to name a few. Clinical care for all preterm infants, however, is focused on reducing short-term and long-term morbidity and mortality and promoting normal growth and development. Human milk not only is a source of nourishment but

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also a life-saving and disease-preventing approach to preterm infant care.[1,2] Compared with formula-fed infants, human milk-fed preterm infants are less likely to develop nosocomial infection, NEC, late-onset sepsis, retinopathy of prematurity, and cognitive impairment.[3,4] Human milk feeding also may be protective against immune-mediated conditions, such as asthma, allergies, and inflammatory bowel disease,[5,6] and chronic noncommunicable diseases, such as cardiovascular disease and type 2 diabetes mellitus, later in life.[6,7] HMOs, the third most abundant component of human milk, may be one of the reasons why human milk supports and protects term and preterm infants.

This review outlines current and rapidly accumulating knowledge on the potential benefits of HMOs for human milk-fed infants and describes how individual HMOs are becoming available for human clinical studies and application.

FOOD FOR THOUGHT: A HUMAN BABY RECEIVES HUMAN MILK OLIGOSACCHARIDES

Milk is a remarkable biological fluid that has evolved over 150 million years to be a crucial source of nutrition and immunoprotection for infants, capable of sustaining life in an often pathogen-rich and nutrient-poor extrauterine environment. It is fascinating that some milk components evolved in a species-specific manner to meet species-dependent biological needs and levels of developmental maturity at term birth. An excellent example of this specificity is the presence of HMOs in milk. HMO structures and composition are far more complex than oligosaccharides in the milk of any other studied species, which includes cow milk on which most infant formula is based and also the milk of humans' closest relatives, nonhuman primates.[8,9] The reason why the human mammary gland invests energy to produce such a high amount and structural diversity of HMOs, with approximately 200 different structures identified so far, is an active area of research. The authors hypothesize that optimal health outcomes associated with HMOs are collectively achieved when infants consume a balanced combination of HMOs, as present in human milk. A particular biological benefit could be due to 1 or several HMOs interacting together. Knowledge of what HMO functions are and which particular HMOs contribute to these functions has increased substantially over the past decade. What a balanced HMO composition in milk is (which might be mother-infant specific), what affects it, and how it relates to infant outcomes, particularly in preterm infants, however, are far from being defined. Human milk components do not optimally meet the developmental needs of preterm infants, and how HMOs in preterm milk contribute to the preterm infant extrauterine metabolic adaptations is not known.

HUMAN MILK OLIGOSACCHARIDES: STRUCTURES, INFANT INTAKE, AND METABOLISM

Structures

HMOs are complex sugars present in free, unconjugated form in the milk aqueous phase. Approximately 200 HMOs with unique structures have been identified to date. HMOs consist of 5 monosaccharide building blocks: galactose (Gal), glucose (Glc), *N*-acetylglucosamine (GlcNAc), fucose (Fuc), and the sialic acid (Sia) derivative *N*-acetylneuraminic acid (Neu5Ac). All HMOs consist of lactose (Galβ1-4Glc) at the reducing end, which can be elongated by the addition of the following disaccharides: β1-3–linked or β1-6–linked lacto-N-biose (Galβ1-3GlcNAc-, type 1 chain) or *N*-acetyllactosamine (Galβ1-4GlcNAc-, type 2 chain). *N*-acetyllactosamine can be further extended by the addition of 1 or more of these 2 disaccharides. A β1-3 linkage between 2 disaccharides results in a linear chain elongation, whereas a β1-6 linkage results in chain branching. Lactose or the elongated/branched oligosaccharide chain