

Human milk oligosaccharides influence development of the microbiome

KEYWORDS: Human milk oligosaccharides, microbiome, gastrointestinal tract, health maintenance, disease avoidance, infant nutrition.

ABSTRACT

Human milk oligosaccharides (HMOs) are a significant component in breast milk and although largely indigestible by infants, they play an important role in infant health and growth by helping to develop the gastrointestinal microbiome immediately after birth. Formula fed infants lack this advantage. The microbiome contains a large bacterial population and harbours an enormous array of genes that allow it to produce many compounds and enzymes which the body cells cannot produce. Nutrition now needs to be directed towards efficient management of the microbiome since it is well established that an optimal functioning of the microbiome will make a major improvement in health maintenance and disease avoidance in later life.

INTRODUCTION

Human milk is the primary source of nutrition for new-born infants and contains, in addition to proteins and fats, a large number of diverse oligosaccharides. These are known collectively as human milk oligosaccharides (HMOs) and comprise between 5 and 23 g/L of human milk. The HMOs are composed of various monosaccharides namely, glucose, galactose, fucose, N-acetylneuraminic acid and N-acetylglucosamine (1). Human milk is unique in that the oligosaccharide content is much higher than in other species. By comparison, the concentration of milk oligosaccharides in goats is 0.25–0.30 g/L, which is higher than in the milk of the cow (0.03–0.06 g/L) or sheep (0.02–0.04 g/L) (2).

Human milk oligosaccharides are largely indigestible by infants, but they play an important role in the health and growth of infants by helping to develop the gastrointestinal microbiome and offer protection against colonization by pathogenic bacteria (3). This is thought to be one explanation for the unique health benefits of breast milk as compared with infant formulas. It is now well accepted that the microbiome has a major impact upon gastrointestinal health and managing the microbiome is crucial for health maintenance and disease avoidance in later life (4).

GASTROINTESTINAL MICROBIOME

The gastrointestinal microbiome is a complex and dynamic ecosystem consisting of several hundreds of species of

different micro-organisms, mainly bacteria (10^{11-12} bacteria/g of colonic content, forming 60% of total faecal mass). The gastrointestinal microbiome influences the growth and differentiation of gastrointestinal epithelial cells, and play pivotal nutritive, metabolic, immunological, and protective functions. Its deregulation, also known as dysbiosis, is involved in the pathogenesis of immunological, cardiovascular, and metabolic diseases (5). Development of the microbiome is an essential requirement to promote immune tolerance and can consequently attenuate or abrogate autoimmune diseases (6).

Over 90% of the bacteria in the microbiome belong to two phyla (major divisions in classification), Bacteroidetes and Firmicutes. Some of the most commonly found genera of bacteria in the microbiome are; *Bifidobacterium*, *Lactobacillus*, *Bacteroides*, *Ruminococcus*, *Clostridium*, *Escherichia*, *Streptococcus* and *Staphylococcus*. Various species of the *Bifidobacterium*, *Lactobacillus*, *Bacteroides* and *Ruminococcus* are generally considered health-promoting, whereas species of *Clostridium*, *Escherichia*, *Streptococcus* and *Staphylococcus* can be pathogenic. Therefore, the balance between the different bacterial species has a major impact upon health. If the normal balance is disturbed this leads to dysbiosis, an imbalance between commensal or harmless micro-organisms and pathogenic micro-organisms.

Another important aspect of the microbiome is the enormous number of genes it contains. There are around 3.3 million genes in the human gut microbiome, as compared to the around 22,000 genes present in the entire human genome (7). Consequently, with this huge array of genes the population of micro-organisms in the microbiome can produce a vast range of products. Fermentation of fibre and protein by bacteria in the large bowel produces short chain fatty acids, acetate, propionate and butyrate, which act as key sources of energy for colorectal tissues and maintain tissue integrity. Short chain fatty acids are also absorbed into the bloodstream and impact the immune function and inflammation in tissues such as the lung. However, some protein fermentation products such as ammonia, phenols and hydrogen sulphide can also be toxic.

Bifidobacterium can generate vitamins such as K, B12, Biotin, Folate, Thiamine (8). Synthesis of secondary bile acids, important components of lipid transport and turnover in humans, is mediated via bacteria such as *Lactobacillus*, *Bifidobacterium* and *Bacteroides*.

Numerous bioactive lipids are produced by bacteria, including lipopolysaccharide, a component of the cell wall of gram-negative bacteria that can cause tissue inflammation. The microbiome is a source of a wide range of molecules which play an important role in health maintenance and disease avoidance.

In addition to the synthesis of many compounds, the genes in the microbiome allow the production of many enzymes which the human body cells cannot produce. This supply of extra enzymes influences digestion and health. Indeed, much of the microbial diversity in the human gastrointestinal tract may be attributed to the spectrum of microbial enzymatic capacity needed to degrade nutrients, particularly the many forms of complex polysaccharides that are consumed by humans and are not digested in the small intestine. The Bacteroidetes are specialized in the breakdown of complex plant polysaccharides and so the introduction of plant derived carbohydrates into the diet would boost populations of Bacteroidetes (9). On the other hand, low levels of Bacteroidetes in the microbiome are correlated with obesity, which itself may result from a diet low in plant-derived polysaccharides. Bacterial phytases of the colon degrade phytic acid present in grains, releasing minerals such as calcium, magnesium and phosphate and making these available to host tissues. Enzymes which degrade mucins help bacteria meet their energy needs and assist in the normal turnover of the mucus barrier lining the gastrointestinal tract (10).

DEVELOPMENT OF THE MICROBIOME

In view of the multiple effects of the microbiome in health and disease, it is important that a beneficial microbiome is rapidly established in the young infant as this plays an important role in lifelong health (11). Although gastrointestinal bacterial colonization begins when a foetus is in the lower uterus, an infant's microbiome is only fully established after birth. During the first year of life, the infant diet is one of the most important factors that shape the microbiome. The influence of diet on microbiome development is clearly illustrated in infants with different feeding routines, namely breast milk feeding and formula feeding. Breast milk feeding promotes infant health by supplying HMOs which guide the proper assembly and activity of the gastrointestinal microbiome (12). Infants lack the enzymes necessary to digest HMOs so most reach the colon unmodified where they can influence the development of the microbiome. In the colon they are fermented, mainly by *Bifidobacterium* and *Bacteriodes* species, to produce short-chain fatty acids. Only a few *Bifidobacterium* and *Bacteriodes* species can use HMOs as the sole carbon source.

Therefore, HMOs have a clear prebiotic effect by selectively stimulating the development of a *Bifidobacterium*-rich and *Bacteriodes*-rich microbiome (13). This is an important benefit from breast milk since inadequate colonization during early childhood may lead to dysbiosis (or an imbalance between commensal

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and pathogenic organisms) which may increase susceptibility to a variety of immune-related pathogenic states (13).

In addition, HMOs are also considered as anti-adhesive antimicrobials (14). To colonize or invade host cells most bacterial, viral or protozoan pathogens need to adhere to carbohydrate structures or receptors on the cells of the gastrointestinal tract. Various HMOs resemble these receptor structures and act as decoys when the pathogenic micro-organisms bind to the HMOs instead of the cells of the gastrointestinal tract. This reduces the risk of viral or bacterial infections since the pathogens are excreted together with the undigested HMOs.

Formula-fed infants lack the benefits of HMOs and exhibit a microbiome with a significant presence of species of *Staphylococcus*, anaerobic *Streptococcus*, and *Clostridium* in addition to *Bifidobacterium*. Some studies have shown that exclusively formula-fed infants are more often colonized with *Escherichia coli*, *Clostridium difficile*, *Bacteroides fragilis* group, and *Lactobacilli* than those that are exclusively breast-fed (13).

Recently, milk formulas have been improved, notably by the inclusion of some HMOs, which makes it possible for a formula-fed infant to establish a *Bifidobacterium*-rich microbiome. However, compared with breast-fed infants, formula-fed infants still have distinctive features of their microbiome such as the overrepresentation of *C. difficile* (15). It is also possible that HMOs could have beneficial effects in adults as well as in infants.

When HMOs were fed to healthy, adults for two weeks, they modified the microbiome, with an increase in abundance of bifidobacteria, to >25% in some individuals (15). This is encouraging since low levels of bifidobacteria have been reported in individuals who are obese or diabetic, taking antibiotics, or suffering from irritable bowel syndrome or inflammatory bowel disease.

CONCLUSION

Supporting the development of an effective microbiome is another, and possibly neglected aspect of human nutrition. Generally good nutrition is directed towards fulfilling requirements for protein, energy, vitamins and minerals in terms of growth of the body. However, nutrition also now needs to be directed towards efficient management of the microbiome as this has an overriding effect upon health maintenance and disease avoidance. In the future we need to ensure that nutrition supplies nutrients for the body but also supplies adequate nutrients for the microbiome in the form of HMOs.

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