Human milk oligosaccharides: Sweet treats not just for kids

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Dr Tanja Šuligoj from the Quadram institute setting up colon intestine chips for fermented HMO testing. Credit: Quadram Institute

Supplements of human milk oligosaccharides (HMOs), the sugars found in breast milk, may help improve the gut health of adults, according to

new research carried out at the Quadram Institute. Using highly advanced 'gut-on-chip' technology, they showed that the fermentation products of HMOs made the gut lining less "leaky." A leaky intestinal barrier has been linked to gut conditions such as coeliac disease, Crohn's disease, and irritable bowel syndrome as well as a range of conditions affecting the rest of the body. This study provides scientific evidence that HMOs may be used to develop strategies to counter these conditions and improve gut health in adults.

Human milk oligosaccharides (HMOs) are complex indigestible sugars naturally present in breast milk. They are particularly interesting because of their quantity and structural diversity, which underpins multiple beneficial benefits to the health babies. They are well-known for their prebiotic effect in infants, where they serve as food for intestinal bacteria, especially bifidobacteria. The dominance of these intestinal bacteria in the gut ensures a healthy intestinal microbiota and reduces the risk of dangerous intestinal infections in infants.

In addition to their demonstrated beneficial role in infant health, a recent clinical trial showed that two specific HMOs, 2'-O-fucosyllactose (2'FL) and/or lacto-N-neotetraose (LNnT), are safe and well-tolerated in adults and are modulators of the adult gut microbiota with an increase in bifidobacteria. This suggests that HMO supplementation may be a valuable strategy to modulate health in adults. However, the impact of HMOs on the gut barrier function has been largely underexplored.

To address this, a collaboration was established between the Quadram Institute, a food and health research center on the Norwich Research Park, UK, and Glycom, a Danish-based biotechnology company and world's leading supplier of HMOs. Their study, published in the journal *Nutrients*, was partly funded by the Biotechnology and Biological Sciences Research Council (BBSRC).

A simulator of the human intestinal microbial ecosystem (SHIME) was used to determine the influence of HMOs on the adult gut microbiota composition and function. These experiments were performed at ProDigest, a spin-off company from the Center of Microbial Ecology and Technology (CMET), located at Ghent University in Belgium. The results showed that fermentation of 2'FL, LNnT and combinations thereof led to an increase of bifidobacteria, accompanied by an increase of short chain fatty acids.

Prof. Nathalie Juge's team in the Quadram Institute then used the products of this fermentation to study the influence of fermented HMOs on the intestinal barrier function of cell lines and advanced gut-on-chip models.

Caco2 cells are a line of cells originally derived from the human gut and used extensively in research, with an arrangement of them into a single layer being an established model for studying the gut and its permeability. A significant reduction in permeability was observed using Caco2 cell monolayers with fermented HMOs, accompanied by an increase in specific proteins known to help maintain barrier integrity, tight-junction proteins and cytokines.

Whilst these results are promising, they still need to be translated into research in humans but studying the interactions at the cellular level inside the gut is very difficult.

To assess the translation of the findings to humans, the team used advanced in vitro models of the human large intestine developed by Emulate Inc, a bio-technology company based in Boston, U.S.. They are specialized in organs-on-chips technology—a human cell-based technology that recreates organ-level function to model organs in healthy and diseased states.

The Intestine Chip is a micro-engineered platform allowing the co-culture of epithelium cells that make up the gut lining with tissue-specific microvascular endothelial cells under microfluidic conditions. This methodology pioneered by Emulate recreates the cellular microenvironment, including tissue-to-tissue interfaces, media flow, and mechanical forces, such as flow and stretch. Through a BBSRC Flexible Talent Mobility Account awarded to Dr. Tanja Suligoj in the Juge Lab, a gut-on-chip system has been established in the Quadram Institute to support translational studies of the gut.

In collaboration with the Norwich Research Park (NRP) Biorepository and the Norfolk and Norwich University Hospital (NNUH), human intestinal biopsies from healthy, consenting adults were used to generate organoids. Organoids are self-organized clusters of cells that grow to replicate tissues of organs—in this case the proximal, transverse and distal regions of the colon. These were then seeded on chips to generate colon intestine chips, which were cultured under microfluidic conditions to recreate the structure and function of the intestinal epithelium. Using this system, they showed a significant increase of certain tight-junction proteins across all three gut-on-chips following treatment with fermented 2-'FL.

Taken together, these data showed that in addition to supporting bifidobacterial growth and a healthy microbiota, HMOs have the capacity to modulate immune function and the gut barrier, supporting the potential of HMOs to provide health benefits in adults.

"HMOs are being used to improve health in infants, as supplements in formula milk, but this work shows the potential application for adults, particularly for those with disorders linked to leaky gut, such as IBS," said Prof. Juge. "More research is needed, particularly in people with the condition we want to treat, but this study also highlights the potential of the gut-on-chip platform as a physiological model, based on human

biopsies, to gain mechanistic insights into gut barrier function."

More information: Tanja Šuligoj et al. Effects of Human Milk Oligosaccharides on the Adult Gut Microbiota and Barrier Function, *Nutrients* (2020). DOI: 10.3390/nu12092808