Milk Alternatives Can Leave Consumers Short on Iodine

- Conventional milk is the primary dietary source of iodine in the U.S. and U.K.
- Organic cow’s milk has only half the iodine of conventional cow’s milk, and milk-alternatives, including soy, almond, and rice milk, have only trace amounts of iodine.
- Consumers who select milk alternatives may need to include a dietary supplement with iodine, especially pregnant and lactating women who have a higher daily iodine requirement.

Milk is well known for being the primary dietary source of calcium, but it may be a surprise to learn that, in the U.S. and U.K., milk is also the leading dietary source of iodine [1-3]. Some of these countries’ consumers are steering away from dairy because of intolerance, allergy, or personal dietary choices. However, researchers have found organic milk [1,4] and milk-alternative drinks like soy, almond, and hemp milk [2,3,5] have only a fraction of the iodine found in conventional milk, indicating that many of those avoiding conventional dairy—especially pregnant and nursing women—may inadvertently be placing themselves at risk for iodine deficiency.

Iodine: Playing Hard to Get

Iodine is a mineral required by humans to produce the thyroid hormones thyroxine and triiodothyronine (or T4 and T3), which control virtually every metabolic and hormonal process throughout the body. During fetal and infant development, these hormones are especially critical for brain and nervous system development. Mild to moderate maternal iodine deficiency during pregnancy can result in impaired cognitive development, and severe maternal deficiency can damage the developing fetal brain and cause mental retardation [6]. The human brain continues to grow at a fetal rate during the first year of life, and thus low iodine in breast milk (due to low maternal intake) is also associated with poor cognitive outcomes [7].

Beyond infancy, iodine deficiency is most commonly associated with goiter. With insufficient iodine to manufacture thyroid hormones, the pituitary gland increases the production of thyroid-stimulating hormone, which in turn causes the thyroid gland to enlarge. Lower than normal production of thyroid hormones (commonly known as hypothyroidism) also slows down all of the body’s metabolic processes. Side effects of these metabolic changes include difficulty staying warm, weight gain, muscle weakness and fatigue, issues with fertility, and even slowed cognitive functioning [6-9].

The Institute of Medicine and World Health Organization (WHO) currently recommend 150 micrograms of iodine per day for adults, 220 micrograms of iodine per day for pregnant women, and 290 micrograms of iodine per day for nursing mothers [3]. A microgram is quite a small unit of measurement—why is it so difficult, then, for people to consume a sufficient amount of iodine? Unfortunately, iodine is as rare in the food supply as it is essential for human health; there are very few foods in which iodine is naturally found. Most of the earth’s iodine is found in the ocean and the richest natural dietary sources of iodine include seafood and seaweed, and plant foods grown in iodine-rich soils near the coasts [8]. As a result, iodine deficiency has historically had a geographic distribution (often referred to as “goiter belts”) [8]. The WHO estimates that 2.2 billion people currently live in iodine-deficient areas (usually inland or high altitude) [8], and iodine is one of the most common micronutrient deficiencies in the world [6].
The accidental ingredient in milk was recognized in the mid 19th century, but it was not until the early 20th century that a solution was identified [8]. In the U.S., iodized salt was first made available in 1924 to people living near the Great Lakes (a well known “goiter belt”), and within a decade was available throughout the U.S. The fortification project was a success, effectively eradicating iodine deficiency and its associated disorders in a matter of years [8].

The story in the U.K. is slightly different. Despite being an island, goiter and other issues related to iodine deficiency were still common throughout Great Britain, even as recently as the early 20th century. The U.K. did not fortify salt with iodine like the U.S. Instead, and rather ironically, the U.K.’s iodine issues were solved by efforts of dairy farmers to improve the health of the country’s cattle. By adding iodine to the cattle’s food, cattle health improved and, as an unintended bonus so did human health [1,9]. Today, it is estimated that milk and dairy foods provide a third of the iodine intake for adults and 40% of the intake for adolescents in the U.K. [2].

Iodine is also an accidental ingredient in milk in the U.S., making its way into milk, and subsequently into other dairy products, because it is in a common cleaning agent used on cow udders and milking equipment and containers [4]. One eight-ounce glass of conventional milk provides approximately 110 micrograms of iodine, just 40 micrograms below the WHO’s recommended daily intake (RDI) for adults [3]. Although iodized table salt is still available in the U.S., dairy foods are the primary source of dietary iodine. Most Americans get their salt from processed foods, which do not contain iodized salt. Moreover, the majority of commercially available iodized salt brands do have sufficient iodine to meet the FDA’s daily requirements [8]. Table salt may have once helped to eradicate iodine deficiency in the U.S., but dairy foods are likely responsible for preventing deficiency today.

Deficiency Déjà Vu?

Iodine in dairy has been called an “accidental public health triumph” [1]. Milk and dairy food consumption were already being promoted in both the U.S. and U.K. for their benefits for bone health, and the benefits from iodine were icing on the cake. But conventional milk has some competition these days, including organic milk, and milk alternative beverages made from soy, nuts, coconut, and rice. Consumers may be driven to these options for environmental, health, (lactose intolerance, milk protein allergy) or dietary preferences (veganism, “Paleo” diet) without realizing that they may not be making an even nutritional swap.

Analyses of organic milk and milk alternatives in both the U.S. and U.K. indicate they contain only a fraction of the iodine of conventional cow’s milk [1-5]. Organic farming regulations limit the use of mineral supplements in cattle feed and in the types of cleaners and materials that are used in milk collection. As a result, organic milks contain between 30% and 45% less iodine than their conventional counterparts, with variation related to season, farm location, and cattle diet [1, 4]. The news is even worse for non-dairy milks. In the U.S., the average iodine content for 30 different brands of milk alternatives (including soy, almond, coconut, cashew, and hemp) was just over 3 micrograms for an eight-ounce glass, which is only 2.7% of the iodine content of cow’s milk [3]. Results were nearly identical (2.1%) when U.K. brands were assayed [2]. Unless these consumers are replacing the iodine from dairy with increased consumption of seafood, seaweed, or an iodine-containing multi-vitamin, they are likely to be falling short of their RDI [2-4].

Interestingly, most milk alternatives are fortified with calcium and vitamin D to approximate that found in cow’s milk—if they can fortify with those important nutrients, why not iodine? Fortification of milk alternatives is not as simple as adding in a few drops of iodine to the mixing bowl, unfortunately. Several of the ingredients used to make milk alternative drinks actually inhibit iodine absorption and reduce the production of thyroid hormones, leading to overproduction of thyroid-stimulating hormone and the growth of a goiter [2,4]. Soy is a well-known goitrogen, and thus adding iodine to soymilk may have no effect on consumer iodine status. Seaweed is actually a commonly used ingredient in milk alternatives to provide calcium and is one of the best dietary sources of iodine. These milks do have more iodine (approximately 40 micrograms of iodine for an 8-ounce serving, compared with 3 micrograms), and yet could still leave consumers with insufficient intake [1-4].
Breastfeeding Associated with Lower Risk for Endometriosis

- Endometriosis, the growth of endometrial tissue outside of the uterus, currently affects 10% of U.S. women and has no known cure.
- A new study based on data from over 70,000 women followed for 20 years found the duration of total and exclusive breastfeeding were associated with a decreased risk of endometriosis diagnosis.
- Breastfeeding lowers the risk of endometriosis through postpartum amenorrhea and other hormonal mechanisms, including suppression of steroid hormones.
- These findings support public policies that encourage breastfeeding for infant and maternal health benefits.

The benefits of breastfeeding are nearly always considered from the perspective of the infant, but breastfeeding also has positive effects on the health of the mother. The hormonal changes associated with lactation may lower the risk of developing many chronic diseases, including breast and ovarian cancer. The results of a new study [1] of over 70,000 women suggest that these same hormonal changes may also lower the risk of developing endometriosis.

Endometriosis is a chronic disorder diagnosed in 10% of U.S. women, but the number affected may be even higher as diagnosis requires confirmation by laparoscopy to rule out other gynecological disorders with similar symptoms, which include painful and heavy periods, and infertility [1]. Despite affecting so many women, endometriosis still has no known cure. Identification of risk factors, particularly those that are behavioral like breastfeeding, is essential in reducing the incidence of this debilitating disorder.

Location, Location, Location

The endometrium is the tissue that lines the inside of the uterus. During the first half of the menstrual cycle, the endometrium thickens in anticipation of a fertilized egg. If no egg attaches, the top layer of the endometrium (called the functional layer) is shed as menstrual blood. Endometriosis occurs if endometrium tissue grows outside of the uterus, usually on the ovaries or fallopian tubes [1]. Having no idea that it is not where it is supposed to be, the endometrium tissue continues along, business as usual, responding to the same hormonal cues in the same manner—thickening in anticipation of a fertilized egg and shedding the top layer if one does not implant. As a result, women with endometriosis generally experience more pain during menstruation and a heavier menstrual cycle.

How does tissue that should only reside in the uterus get to the ovaries and fallopian tubes? The leading hypothesis to explain endometriosis is retrograde menstruation, which is the movement of menstrual
blood, containing endometrial tissue, into the fallopian tubes, ovaries, and even the pelvic cavity. It is still not well understood, but a small amount of retrograde menstruation may occur as a normal part of each menstrual cycle [1]. Development of endometriosis depends on how much endometrial tissue ends up in the wrong location—more menstrual cycles mean more retrograde menstruation, and thus a greater risk for developing endometriosis [1-4].

Factors that increase the number of periods a woman experiences, such as an earlier age at menarche (≤11 years old) and shorter cycle length (≤27 days), are associated with an increased risk of developing endometriosis [2]. On the other hand, factors that decrease the number of periods, including pregnancy and lactation, have the potential to reduce the risk [1,2].

During pregnancy, high levels of circulating estrogen and progesterone suppress the hormones (i.e., follicle stimulating hormone, or FSH, and luteinizing hormone, LH) that trigger ovulation. Moreover, the implantation of a fertilized egg in the endometrium means that tissue stays right where it belongs. The relationship between breastfeeding and ovulation is less clear-cut, however. “You can’t get pregnant while you are breastfeeding” may be one of the most common pieces of advice given to new mothers, but it is not entirely accurate advice. Breastfeeding can suppress ovulation, resulting in amenorrhea (lack of menstruation) and temporary infertility. But just how long a mother remains infertile while breastfeeding varies with respect to nursing frequency and intensity, as well as maternal condition. Infant suckling suppresses the production of FSH and LH, thereby inhibiting ovulation and menstruation. However, the stimulus from infant suckling must be consistent in order to suppress these hormones at levels sufficient to prevent follicular development and subsequent ovulation [5]. Thus, lactational amenorrhea requires frequent nursing (approximately every 3–4 hours), like that associated with the earliest months of lactation (< 6 months) before solid foods are introduced [5].

Lowering the Risks

Based on the relationship between breastfeeding and amenorrhea, a team of researchers from Harvard, UCLA, and Michigan State University hypothesized that, among women who have been pregnant, the duration of breastfeeding would be associated with a lower risk of developing endometriosis [1]. Specifically, they predicted that the strongest protective effects would be associated with the duration of exclusive breastfeeding (i.e., milk is the only source of nutrition) and lactational amenorrhea [1].

Data to test their hypothesis came from the Harvard-based Nurses’ Health Study II, one of the largest prospective cohort studies on risk factors for disease in U.S. women. Over 100,000 female nurses were originally enrolled to provide information on diet, lifestyle, and health via questionnaires provided every two years. The current study on breastfeeding and endometriosis included 72,394 women who had reported at least one pregnancy lasting at least 6 months between 1989 and 2011. Of these, 3,296 had endometriosis that was confirmed by laparoscopy [1]. This is the largest study to date to address the relationship between breastfeeding and risk of endometriosis.

When looking at the total duration of breastfeeding across their lifetime, women who breastfed for 36 months or more had a 40% lower risk of an endometriosis diagnosis compared with women that never breastfed. For every additional three months of lifetime breastfeeding, the risk decreased an additional 3% [1]. The results when considering individual pregnancies were similar to those looking at the total duration of breastfeeding; for every additional three months a mother breastfed an individual infant, her risk of endometriosis diagnosis dropped by 8% [1]. The protective effect of exclusive breastfeeding was even more dramatic. For each pregnancy, there was a 14% decreased risk of endometriosis for each 3-month increase in exclusive breastfeeding.

Exclusive breastfeeding has a biologically defined endpoint—as human infants grow, their metabolic needs require provisioning with foods other than breast milk sometime around 6 months of age. Thus, it is
extremely important that this study found breastfeeding after solid food introduction still offered a significant protective effect [1]. Moreover, this study identified an inverse linear relationship between breastfeeding duration and risk of endometriosis; rather than plateau out at some point during lactation, risk continued to decrease with each additional three months of nursing.

Taken together, these findings suggest that factors other than postpartum amenorrhea are responsible for the protective effect of breastfeeding on endometriosis. To this end, the study [1] found the duration of postpartum amenorrhea was inversely associated with risk of endometriosis and explained a significant proportion—but not all—of the risk reduction that was associated with total lifetime duration of breastfeeding and exclusive breastfeeding.

Equally important to considering retrograde menstruation is an understanding of the mechanisms that control this tissue’s ability to adhere, proliferate, and survive outside of the uterus [1]. Supporting this, a study [6] on rats with surgically induced endometriosis found that although endometrial lesions progressed during pregnancy, no lesions progressed during lactation.

The hormonal profiles of breastfeeding women, even those no longer experiencing amenorrhea, are different from non-nursing (or non-pregnant) women [1,4]. Notably, breastfeeding women have higher circulating levels of oxytocin and prolactin and lower levels of estrogen and progesterone [1,4]. These hormonal changes are believed to offer protective effects on the growth of breast and ovarian cancers and may play a similar role in limiting the growth of endometrial tissue [1,4].

Next Steps

Breastfeeding does not prevent endometriosis. And it is not a cure. But the findings of this prospective cohort study of over 70,000 women suggest it is a significant factor in the development of this disorder and may even play a role in lessening or alleviating symptoms in breastfeeding women with endometriosis [1].

The takeaway from these findings is not to simply tell all women to breastfeed and to do so for as long as possible. The world we live in is not structured in such a way that this is achievable for all women (or even for most women). Policy must follow the science. When study after study continues to demonstrate the health benefits of breastfeeding (for both mother and child), there should be some response in policy to encourage and support breastfeeding across the population (e.g., longer maternity leave, private and hygienic pumping stations at places of work). This type of research should not make those that are unable to breastfeed feel inadequate, but rather it should encourage action to level the playing field so that all mothers can improve their health outcomes.


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Donor Milk Research: A Conversation with Sharon Unger

- Ontario’s human milk bank opened five years ago. It has since been involved in a number of clinical trials into the potential developmental benefits of donor milk to infants.
- The Greater Toronto Area (GTA)-DoMINO trial found that among preterm infants whose mothers were unable to produce sufficient milk, those fed a bovine milk-based formula had an increased risk of necrotizing enterocolitis compared with those fed donor milk.
- More recently, the participants in the GTA-DoMINO trial have been invited back, at age five, so that more detailed and long-term neurodevelopmental and other outcomes can be measured.
Sharon Unger is a neonatologist who conducts trials on the developmental outcomes of preterm infants who are fed donor milk. She works closely with Debbie O’Connor, a dietitian scientist also based in Toronto. Together they chair the Advisory Committee for the Rogers Hixon Ontario Human Milk Bank and are the principle investigators of the OptiMoM and MaxiMoM Programs (Optimizing and Maximizing Mother’s Milk). Here Sharon talks to SPLASH! about those studies.

How is donor milk processed?

The process begins with screening potential milk donors in a similar way to how blood donors are screened. There’s an interview, a consent process, and a blood analysis. Once approved, a milk donor—we call them “donor mothers”—collects her milk until she has about five liters to give away. Her milk is then taken to a milk bank for processing. There, milk from four different mothers is pooled, before it is pasteurized and eventually bottled. The pooling makes for a more average composition of donor milk. Most milk banks pasteurize by heating milk to 62.5ºC for 30 minutes—a technique called Holder pasteurization. Before the milk is bottled, it’s cultured to check no germs survived pasteurization.

What motivated you to start running trials on donor milk?

In the intensive care unit, 70% of preterm babies don’t have a full supply of their mother’s milk. Until just a few years ago, we used to make morning rounds and would ask the moms, “Do you have any milk yet?” If they said no, we’d leave the babies with nothing to eat for up to 96 hours because we didn’t want to give them a bovine milk-based formula (it’s known to increase the risk of severe inflammation of the gut, necrotizing enterocolitis). That was stressful for everybody—for the baby, the staff, and particularly stressful for the mothers. With every cell [in their bodies] they want to provide nourishment for their babies, but often mothers feel too much pressure and it becomes a vicious cycle. So, we needed a better alternative to bovine milk-based formula. But to set up a donor bank we needed evidence. In Canada’s socialized medicine system, you have to prove that something’s of benefit before you can ask for the money.

So, there was no milk bank in Ontario until a few years ago?

Until 2013, no. There had been one here for a long time previously. It shut down in 1985 when we learned that HIV could be carried in human milk. All the milk banks in Canada shut down then except for the one in Vancouver. That meant almost all of the evidence for the benefits of milk banks within the Canadian health system was 30 years old.

Your first big donor-milk study was GTA-DoMINO. What did it find?

DoMINO stands for Donor Milk for Improved Neurodevelopmental Outcomes. We randomized very-low-birth weight babies—those weighing less than 1,500 g at birth—to receive either donor milk or a bovine milk-based formula if their mothers were unable to produce enough milk. Our primary outcome was the neurodevelopment of these infants at 18 months after their due date. We tested their cognitive, language and motor development.

We did what is called an “intention-to-treat analysis”—a kind of statistical approach—that didn’t find an effect on the primary outcome. But this way of looking at the data includes all of the infants in the trial whether they required a supplement to mother’s milk or not. Of course, the infants whose mothers did
produce sufficient milk, which was 30% of the total, had better cognitive development when they were analyzed separately.

The really significant result from DoMINO was a big difference in the incidence of necrotizing enterocolitis, which is where the gut becomes inflamed and can start to die. It’s a really dangerous problem for preterm infants. Canada has a low rate of necrotizing enterocolitis among preterm infants, with just 6% to 7% of them developing it. That’s very low compared to what you see in the literature. The donor milk-fed preterm infants in the DoMINO trial had a rate of about 1.7%—much lower than the bovine formula-fed preterm infants in the trial.

**How have your subsequent trials built on these results?**

We’ve been very fortunate to receive funding to invite the same children back when they reach five years old—to see if receiving a bovine milk-based formula as a preterm infant has long-term developmental impacts. These children are currently turning five, so we don’t have all the results yet. It’s important because you can imagine that doing cognitive tests on 18-month old infants can be quite challenging, especially if the infant has separation anxiety. In the OptiMoM trial, we’re now testing cognitive development at age five in really detailed ways, including using an MRI scanner.

We also have a trial testing the developmental effects of different donor milk fortifiers. The growth of a baby is at its most rapid in the third trimester of pregnancy. This is what the very-low-birth weight infants have missed out on. So they need a much higher dose of protein and other nutrients than infants born at term. There’s one product on the market now where the fortifier is made from donor milk. So we’re comparing the outcomes associated with receiving donor milk plus this fortifier with donor milk plus a bovine milk fortifier.

Together, these trials mean that we have a really large biobank of all kinds of samples—mother’s milk, donor milk, stool samples. Now we’re adding to it buccal swab samples from the five-year olds.

**What are the main challenges in running trials with preterm infants?**

These trials are tough to do. It’s particularly tough to keep them blinded because every nurse will guess what a baby is being fed. So, we have had diet technicians prepare our feeds away from the intensive care unit, and put the feeds into an amber-colored syringe with all of the tubing attached. This way the nurses can’t see or smell the feed.

**Trials on preterm infants usually involve a very small number of participants. How many infants have been enrolled in these trials?**

We had 363 preterm infants in the GTA-DoMINO trial and have followed more than 90% of those who survived until they reached two years old. We’re hoping that we’ll see at least half of those back as five-year olds. And then in the fortifier trial, we had 127 preterm infants.

**In an ideal world, for how long would you like to follow the GTA-DoMINO participants? Some studies that look for IQ differences in mother’s milk-fed and formula-fed term infants have run until the participants were in their 20s or 30s.**

Right now, we only have funding for the study on five-year olds. It would be great to continue for longer, but I think that’s going to depend on whether we see developmental differences at five years.

**Are you also testing methods of donor milk pasteurization other than Holder pasteurization?**

In the lab of my Co-PI on these projects, Debbie O’Connor, we are looking at different non-thermal methods like ultraviolet light and high pressure to pasteurize donor milk.

On that matter, in the future, it would be interesting to compare donor milk that is pasteurized differently, given all the immune proteins and digestive proteins that can be damaged by Holder pasteurization. I think there will be more options for donor milk and human milk-based fortifiers in the years to come,
which might give us different processing methods to compare. There’s going to be a lot of work on how to best fortify mother’s milk and donor milk for preterm infants. It’s a whole up-and-coming area of research.

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Synthesizing the Complex Sugars in Human Milk

• Sugars in human milk, called human milk oligosaccharides (HMOs), are associated with many beneficial effects, and as a result researchers have been attempting to synthesize these sugars.

• So far, researchers have mainly been able to synthesize relatively simple HMOs, but a new study describes a way to synthesize a wide variety of structurally complex HMOs.

• The study finds that the complex structures of HMOs affect how proteins bind to them, suggesting that these structures play an important role in the biological activity of HMOs.

Human milk is rich in sugars, called oligosaccharides, which have been associated with many beneficial effects [1,2]. These human milk oligosaccharides (HMOs) form the third-largest component of human milk, and are known to modulate the immune system, protect against pathogens, and help establish the gut microbiome [3-9].

Given their beneficial effects, it’s no surprise that researchers have been interested in synthesizing HMOs for their potential to be used as nutraceuticals or therapeutics. In the past decade, they have developed a variety of methods to synthesize these sugars [10,11]. But despite having identified hundreds of HMOs so far, researchers have only been able to synthesize a small number of them in large quantities, and the synthesized HMOs tend to have relatively simple structures.

“Most of the research dealing with human milk oligosaccharides, especially synthetic ones, mainly deals with relatively small oligosaccharides,” says Geert-Jan Boons, Professor of Chemistry at the University of Georgia. “But if you look at the composition of human milk oligosaccharides, there are also highly complex molecules,” he says. “To make these very complex branched structures, there are no synthetic methodologies yet,” says Boons. One alternative to synthesizing complex oligosaccharides is to extract them from cow milk or human milk by fractionation. Although this technique has been helpful for trying to replicate the diversity of HMOs found in human milk, it’s not as useful for isolating well-defined individual HMOs.

Without the ability to isolate well-defined HMOs with complex structures, there’s still a lot we don’t know about how their structural complexity affects their biological activity or their potential to be used as therapeutics or nutraceuticals. “I’ve always had an inkling that there must be something to these complex structures,” says Boons. “My suspicion was that there would be major differences in their biological activity,” he says. Boons and others have thus been looking for ways to synthesize complex HMOs in sufficient quantities to investigate their biological mechanisms. “We have been thinking of these issues for a long time, and have been working on chemo-enzymatic approaches,” he says.

In a new study, Boons and his colleagues describe a chemo-enzymatic strategy to synthesize a wide array of complex HMOs [12]. They previously used a different chemo-enzymatic approach to make asymmetric N-linked glycans [13]. “In the new study, we take it one step further, and through relatively simple enzymatic transformations we make highly complex, well-defined human milk oligosaccharides,” says Boons. “This is a wonderful tool for exploring the importance of human milk oligosaccharide complexity,” he says. The researchers found that the complex structures of HMOs affect how different proteins bind to them, suggesting that these structures play an important role in the biological activity of HMOs.

The new synthesis approach relies on a particular enzyme, N-acetyllactosaminide β1,6-N-acetylglucosaminyltransferase, or GCNT2, which is responsible for creating branch points in the HMO structure. “The key feature is that we identified the branching enzyme,” says Boons. “If we install the
branching point at the right step in synthesis, one arm can be extended while the other arm is not,” says Boons. This allowed the researchers to build complex asymmetric HMOs step-by-step, using a combination of glycosyltransferase and hydrolase enzymes. “Exploiting these enzymes that make human milk oligosaccharides can provide additional levels of control,” says Boons.

As a proof of principle, the researchers exploited the inherent selectivity of glycosyltransferase and hydrolase enzymes to create a library of 60 highly diverse HMOs with complex structures, which they used to develop a glycan microarray. They then used this microarray to test whether complex HMO structures led to differences in protein binding.

Boons and his colleagues tested the binding of three glycan-binding proteins: a protein involved in immune modulation, a Vibrio cholera toxin and an adhesion protein from rotavirus, a virus that can cause gastroenteritis and diarrhea in infants. “The results turned out to be very dramatic, even more dramatic than I had anticipated,” says Boons.

The researchers found that complex HMO architectures had a large influence on how proteins recognized them, and the complexity of HMO structures affected the selectivity of protein binding in unanticipated ways. “The more complex branched structures are much more potent ligands compared with the simple oligosaccharides,” he says. This suggests that it’s not just the terminal oligosaccharide motifs but the entire oligosaccharide structure that mediates protein recognition. “I think we’re beginning to get a handle for why these complex human milk oligosaccharides exist; because they’re much better ligands,” says Boons.

The new technique could provide researchers with a valuable tool to study HMOs. “Now at least we will have the ability to research almost every possible human milk oligosaccharide,” says Boons. “Our study is a proof of principle, but hopefully it will serve as motivation for others to conduct more studies on these complex molecules,” he says.

The newly-developed synthesis technique is well suited to studying the biological activity of individual HMOs, to find out which ones are beneficial and determine their functions. “The beauty of chemical synthesis is that it is replenishable, we can scale it, and we can get materials of very high purity, so we can have confidence in testing biological activity,” says Boons. “We can make one change at a time to tailor-make a molecule, so we can look at the structure-activity relationship of a particular molecule in isolation,” he says.

In the future, Boons is planning to create a much larger collection of HMOs and use them in additional glycan microarrays, which he hopes will help the research community study how these molecules behave in different biological systems. “We want to move this field into the ‘omics’ era, where we can quickly look at large numbers of oligosaccharides,” he says.

Being able to quickly study a wide variety of complex HMOs could help researchers identify HMOs that are useful as nutraceuticals or as therapeutics. “I think we now have the tools to go hunting for which human milk oligosaccharides should be included in things like baby formula,” says Boons. However, using the new technique to produce HMOs at a very large scale for commercial purposes is likely to be very expensive. “I see this as a discovery tool for human milk oligosaccharides,” says Boons. “If we know the ones that are important, we can use other methods to synthesize them,” he says.

Someday we might be able to use some of these complex HMOs in baby formula to make it more closely resemble human milk, but there’s still a long way to go. “I don’t think we are close to recreating human milk, but maybe we can identify a handful of molecules that resemble the pool of human milk oligosaccharides in human milk,” says Boons. “We’ll still have to do clinical studies, which is a slow process, but now at least we can see a path forward,” he says. “The hope is that this brings us one step closer,” says Boons.


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