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THIS ISSUE

Milk Oligosaccharides and Infant Formula

The benefits of breastfeeding for both mother and baby are well accepted among the healthcare profession. Breast milk provides unique nourishment for the infant, the composition of which changes over time, adapting to the changing nutritional requirements of the growing and developing infant.

In addition to the provision of basic nutrition, breast milk is also associated with other health-promoting functions and components. Indeed, research on human milk oligosaccharides is gaining significant interest as evidence relating to their biological functions increases. Such biological activities are discussed further in the Expert Review (pages 2 and 3).

However, breastfeeding is not always possible, or parents/carers may make an informed decision not to breastfeed their baby. In such cases, a suitable infant formula should be chosen. Infant formulas are developed with the aim of reproducing, as best as possible, the composition of breast milk. Saying that, the composition of infant formula milks does not match that of natural breast milk. Efforts, therefore, continue to focus on the development of ingredients to improve infant formula.

While human milk oligosaccharides may, potentially, represent attractive functional ingredients in relation to infant formula, a key obstacle in such research is the limited availability of the required amounts for necessary clinical or intervention trials. Consequently, among the ongoing work within this area, research is exploring alternative sources of functional oligosaccharides.

Within Food for Health Ireland (FHI), researchers are evaluating oligosaccharides from bovine milk as potential novel, functional ingredients for use in infant formula. This work was initiated as part of FHI Phase 1. The FHI early infant nutrition research programme links specific market opportunities with scientific expertise available in Ireland.

FHI Phase 2 was officially launched by Richard Bruton, Minister for Jobs, Enterprise and Innovation, in November 2013. As well as the infant nutrition programme, research is underway in appetite modulation, performance nutrition and healthy ageing, in addition to a programme entitled healthy cheeses and a programme focusing on the development of products, which can be used to manage elevated glucose levels like in type 2 diabetics. Through the research, conducted by scientists at UCD, UCC, UL, Teagasc, NUIG, NUIM and DCU, FHI is bringing an array of promising ingredients into this second phase of the work and an important part of the funding will be used to conduct human intervention studies to test the health benefits of these ingredients. The intention is to have products on the market so consumers can reap the benefits of this research.

Pictured at the official launch of FHI Phase 2 at the Enterprise Ireland Technology Centre Expo in November 2013 are: Jens Bleiel, CEO Food for Health Ireland; 6 month-old Alyssa Flynn; Richard Bruton, Minister for Jobs, Enterprise and Innovation; and, Olympian Dr Ronnie Delany.

"Through the collaboration with the National Dairy Council (NDC) on this publication, we aim to ensure both health professionals and industry experts remain informed of projects and developments within each FHI work programme, assisting with the application of evidence to practice," says Jens Bleiel, CEO of FHI.

EDITORIAL

Welcome to the first issue of *DN Forum* for 2014!

As *DN Forum* enters its second year as a collaborative publication with FHI, we are extremely pleased with the feedback received regarding the new format and approach. We are delighted this publication is meeting the expectations of our readers, and we look forward to sharing three exciting editions with you throughout 2014.

In this edition, the spotlight is on milk oligosaccharides. The Expert Review – written by Dr Mariarosaria Marotta, Dr Jonathan Lane and Dr Rita Hickey, FHI resesarchers based in Teagasc Food Research Centre Moorepark – provides an overview of the current understanding of the role of milk oligosaccharides in human health, as well as highlighting current research being conducted within FHI that aims to contribute to the evaluation of bovine milk oligosaccharides as potential functional ingredients for infant formula.

In addition, exciting developments resulting from the establishment of FHI Phase 2 are summarised in the main article on page 1, while some of the varied and wide-reaching events scheduled to take place during National Dairy Week are presented on page 4.

As always, please continue to get in touch with any feedback or suggestions: nutrition@ndc.ie

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Milk's Hidden Treasures: the Role of Oligosaccharides in Human Health


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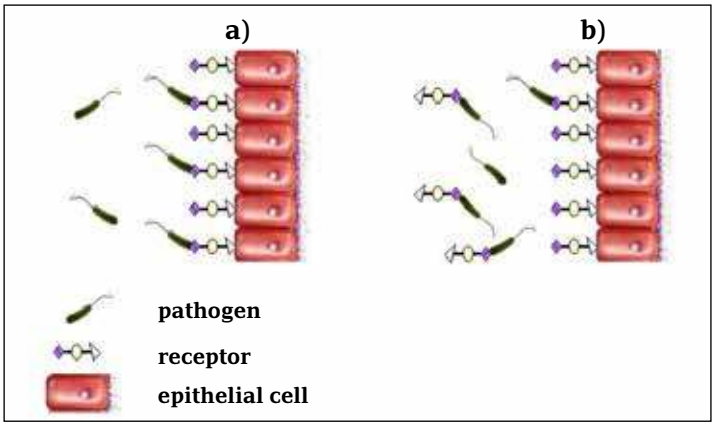
Introduction

Breast milk has evolved to nourish human infants, hence the phrase 'breast is best'. The World Health Organisation recommends to exclusively breastfeed infants for the first six months of life, given the accumulating evidence that exists on the benefits of breastfeeding for growth, development and health[1]. It, therefore, is no surprise that milk is linked to functions beyond basic nutrition. Recently, among the many milk components identified, human milk oligosaccharides (HMO) are gaining increased interest as important bioactive molecules. In fact, HMO have been implicated in a number of important biological functions that benefit the infant, such as prebiotic activity, defence against bacterial and viral infections, modulators of cell surface carbohydrates and immune system responses, all properties that are dependent on their chemical structures. However, breastfeeding is not always possible, which has led researchers to investigate the possibility of adding these valuable molecules to infant formulas in an effort to emulate the nutritional content of breast milk. Of course, human milk is not a commercially viable source of milk oligosaccharides and thus, researchers have been challenged with identifying alternative sources of functional oligosaccharides. Indeed, researchers within Food for Health Ireland (FHI) have been developing a programme focused on health-promoting oligosaccharides found in bovine milk.

Biological activities of milk oligosaccharides

Oligosaccharides are the third largest solid fraction of human milk following lactose and lipids, with concentrations reaching up to 50g/L or more in colostrum to an average of 10-15g/L in mature milk[2,3], while the concentration found in bovine milk is far less. The core structures are based on lactose, which is modified by the addition of specific monosaccharides such as N-acetylglucosamine, galactose and/or fucose (neutral oligosaccharides), or acidic components such as N-acetylneuraminic acid, also called sialic acid (acidic oligosaccharides)[4]. Moreover, their chemical structure influences their biological activities. Given that a number of bovine milk oligosaccharides (BMO) are structurally similar to certain HMO, with some structures common to both human and bovine milk[5,6], it is likely that BMO would also have similar biological functions.

One of the first functions attributed to HMO was their prebiotic or bifidogenic effect, which results in modulation of the infant's intestinal microbiota composition[7-9]. Furthermore, other *in vitro* studies have indicated that specific HMO, mainly acidic, may have an effect on the immune system[10-12]. Investigations on both HMO and BMO have identified additional biological activities associated with these carbohydrates. For instance, 3'-sialyllactose may modulate the expression of glycans on epithelial cell surfaces *in vitro*. These surface glycans can act as attachment sites for commensal and pathogenic bacteria, therefore modulation of their expression could, in turn, modulate bacterial colonisation[13]. One of the most characterised properties associated with both HMO and BMO is their anti-infective potential. HMO are considered to act as soluble receptor analogs of epithelial cell surface carbohydrates[14]. These oligosaccharides display structural homology to host cell receptors and thus function as receptor decoys, which pathogens can bind to instead of the host, as illustrated in **Figure 1**. As a consequence of this interaction invading pathogens fail to colonise the epithelia, which prevents the emergence of disease. For instance, fucosyloligosaccharides have been shown to inhibit *Campylobacter jejuni* infection *in vitro*[15] and provide protection against the heat-stable toxin of *E. coli in vivo*[16]. A number of studies have shown that BMO may have similar properties as demonstrated in anti-infective studies against *Helicobacter pylori* (*in vitro* and *in vivo*)[17,18], *Neisseria meningitides* (*in vitro*)[19] and influenza virus (*in vitro*)[20,21]. Indeed, the group at Teagasc has shown that BMO can reduce *Campylobacter jejuni* invasion into human colonic epithelial cells[22]. Also, researchers have investigated the ability of individual oligosaccharides, which are found in both human and bovine milks, in preventing, for example, the colonisation of *Pseudomonas aeruginosa in vitro*[23] and of *Streptococcus pneumoniae* using both *in vitro* and *in vivo* models[24,25]. Similarly, 6'-sialyllactose, which is found in human and bovine milk, was shown by the group at Teagasc to increase the adherence phenotype of *Bifidobacterium longum subsp. infantis* suggesting that milk oligosaccharides, in addition to preventing pathogen colonisation, can promote colonisation of beneficial commensal organisms[26]. Human gene expression analyses were also performed by the Teagasc group and revealed that human colonic epithelial cells exposed to human and bovine milk oligosaccharides responded in a similar manner. Both treatments had potential effects on similar cellular processes, including a response to stimulus, signalling, locomotion, multi-cellular organismal processes, developmental processes, and immune system processes[27]. Overall, the research outputs at Teagasc highlight the potential of bovine milk as a suitable source of oligosaccharides that may function similarly to those found in human milk.



▲ Figure 1. Ability of HMO to prevent infection: antiadhesive effect. a) Pathogenic bacteria bind to carbohydrate receptor on epithelial cells, causing infection. b) HMO mimic the carbohydrate receptors on the epithelial cells and block the bacteria from binding.

Implications for future research

In recent years, to overcome the issue of HMO availability, commercial oligosaccharides such as galactooligosaccharides (GOS, enzymatically synthesised from lactose) and fructooligosaccharides (FOS, of plant origin), which have been shown to exert prebiotic activity, are currently added to certain products such as infant

formulas[28]. However, these oligosaccharides lack the complexity and diversity of HMO and are unlikely to exert all the beneficial effects ascribed to HMO[28]. Teagasc researchers in FHI, for this reason, have begun to investigate oligosaccharides from bovine milk given the wide availability of this milk and its by-products. More importantly, as mentioned, the oligosaccharides in bovine milk are more similar in structure to HMO in comparison with commercial oligosaccharides on the market. However, because bovine milk contains only trace amounts of these valuable components (**Table 1**), the use of dairy streams, in particular derived from whey, is an attractive option for large-scale extraction. The advantage of using specific whey fractions stems from their wide availability and low cost compared to other dairy streams. The oligosaccharide team in FHI, led by Dr Rita Hickey, is currently investigating/researching processes for producing BMO from whey streams with a view to industrial-scale production. Furthermore, through FHI, the team is investigating the anti-infective potential of BMO *in vitro* on respiratory bacteria and viruses based on results obtained in the first phase of FHI, which demonstrated the ability of 6'-sialyllactose (a predominant oligosaccharide in human and bovine milk) to reduce the invasion of *Pseudomonas aeruginosa* in human pneumocytes[29]. Studying respiratory pathogens is of particular interest given that almost 50% of all paediatric consultations in industrialised countries are associated with respiratory tract infections[30]. Moreover, acute otitis media (aetiological agent *Streptococcus pneumoniae*) is one of the most frequent childhood diseases and prevention of infection is largely difficult.

Mammal	Colostrum	Mature milk
Human	20-50	10-15
Bovine	0.7-1.2	0.05

▲ Table 1. Concentration (g/L) of oligosaccharides in human and bovine colostrum/milk.

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EVIDENCE TO PRACTICE
Significance of this research to:

A. INDUSTRY
BMO are naturally present in whey as a by-product of cheese or casein production. While whey, in itself, is a valuable dairy stream for extraction of whey proteins, its by-products, which contain milk oligosaccharides, are mainly considered waste streams. Production of oligosaccharides from whey streams would result in the production of high value-added ingredients from low-cost products.

B. HEALTH PROFESSIONALS
A deeper understanding of the health benefits of HMO and BMO would help health professionals to highlight and provide advice on the consumption of infant formulas containing milk oligosaccharides, once available on the market, where breastfeeding is not possible.

C. THE PUBLIC
Educating people on the importance of the benefits of breastfeeding for growth, development and health of newborns is essential. However, it is equally important that the correct information is available regarding infant formulas and their ingredients in order to aid parents and carers to make informed decisions, when breastfeeding is not possible.

Key Points - from the Expert Review

- Early nutrition is key for the optimal growth and development of infants. The benefits of breast milk have been documented extensively. However, although breastfeeding is recommended, it is not always possible and, consequently, infant formulas are used instead.
- Infant formulas from bovine milk are formulated to match the nutritional properties of human milk. However, infant formulas, while very advanced, are not perfect substitutes of human milk.
- Recently, human milk oligosaccharides have been shown to exert several health benefits. However, concentration of oligosaccharides in bovine milk and, consequently, in infant formulas is low.
- Adding milk-derived oligosaccharides to infant formulas could be of benefit, once their health benefits have been further elucidated. With this in mind, Food for Health Ireland is working to develop a process for enriching oligosaccharides from whey streams, while investigating their biological properties.

National Dairy Week – 12th to 18th May, 2014

Following the success of National Dairy Week 2013, this year's week-long celebration of all things dairy will commence Monday, 12th May. This year, the campaign coincides with the 50th anniversary of the National Dairy Council. Commencing with the launch of the NDC Kearney Brothers advertising campaign on Friday, 9th May, the following activities will have national and regional media coverage:

Date	Event	Venue/Platform	Partner
Friday, 9th May	Launch of National Dairy Week in association with SuperValu	The Late Late Show, RTÉ One Television	
Monday, 12th May	Dairy Education - *'From Farm to Fridge'* for primary schools	Family Farm, developed by Agri Aware and Dublin Zoo	
Tuesday, 13th May	DairyFest	Dublin City Centre	
Tuesday, 13th May	Symposium for dietitians focusing on Dairy Protein & Healthy Ageing	Clyde Court Hotel, Dublin	
Wednesday, 14th May	NDC Annual Conference	RDS, Dublin	
Thursday, 15th May	NDC Milk It Advertising Awards Final	Mansion House, Dublin	

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Mission: To deliver real and unique value to Irish dairy farmers by protecting and promoting the image, quality, taste and nutritional credentials of Irish dairy produce to a wide variety of audiences in a clearly defined, focused, unique and effective manner.

FOOD FOR HEALTH IRELAND (FHI)

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Mission: To leverage the world-class capabilities of the Irish academic partners, with the market expertise of the industry partners, into a pipeline of innovative, nutritional functional ingredients/products for the global food industry.