The milk-based diet of infancy and the gut microbiome

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Abstract

The composition and the diversity of the gut microbiome play a major role in the health and well-being of humans beginning at birth. The impact of the diet on the structure and the function of the gut microbiome is evident by the changes in the gut microbiome concurrent with the transition from human milk to solid food. Complex oligosaccharides contained in milk are essential nutrients for commensal microbes in the infant gut. The most important commensal bacterium in the infant gut, bifidobacteria, requires α1, 2 fucosylated oligosaccharides for growth. Because not all humans are able to secrete α1, 2 fucosylated oligosaccharides into milk, the gut microbiome of infants and bifidobacteria, in particular, vary considerably between ‘secretors’ and ‘non-secretors’. A paucity of α1, 2 fucosylated oligosaccharides and bifidobacteria in the gut of infants may be associated with poor health.

Key words: Gut microbiome; oligosaccharides; secretors; non-secretors; bifidobacterium

Introduction

The composition and diversity of the gut microbiome play a major role in the health and well-being of humans beginning at birth. Health benefits attributed to the gut microbiome include behavior, cognition, socialization, coordination, immunity/host defenses, and protection against diabetes, obesity, inflammatory bowel disease, infectious diarrhea, and colon cancer [1–9]. During the first 3 years of life, the gut microbiome is in a continuous state of change [6]. At birth, the gut of newborns born via the vagina quickly becomes colonized with bacteria from the vagina and rectum of their mothers; however, the gut of newborns born via cesarean section mainly becomes colonized with bacteria from skin of their mothers [10, 11]. The newly acquired gut microbiota begins to change under the influence of a milk-based diet [12]. Breast milk and/or infant formula constitute the infant diet for most of the first year of life [13, 14]. Human milk and cow-milk formula are linked to bifidobacterium colonization. Bifidobacteria become dominant members of the gut microbiota regardless of whether the child consumes human milk or formula; however, bifidobacteria are more prominent in the breastfed child [15].
**Human milk vs cow-milk formula**

The American Academy of Pediatrics recommends exclusive breastfeeding for the first 6 months of life and the gradual addition of solid food during the succeeding 6 months of the first year; however, only 25% of infants in the USA achieve this goal [16, 17]. The majority of infants will be switched to the cow-milk-based formula. However, human milk and cow milk are very different in composition. They contain different types and quantities of fats, carbohydrates, and proteins. The difference between oligosaccharide carbohydrates in human milk and cow milk is significant and is responsible primarily for differences in the gut microbiome. There are more than 250 different types of oligosaccharides in human milk and not all have been identified, much less synthesized. The amount of oligosaccharides in human milk is 20–1,000-fold more than in cow milk and with a far greater variety. Manufacturers of infant formula have made significant strides in producing a commercial formula that closely resembles human milk. However, synthesizing human complex oligosaccharides has proven difficult. Currently, manufacturers of infant formula have fortified some but not all formulas with commercial galactooligosaccharides (GOS), polydextrose, and fructooligosaccharides in an attempt to mimic human milk [17, 18]. There is some evidence that GOS in infant formula functions in the infant gut in a manner similar to human milk oligosaccharides [19].

**Milk oligosaccharides**

Complex oligosaccharides are short chains of 3–15 sugars and contain glucose, galactose, fucose, N-acetylglucosamine, and N-acetyl-neuraminic acid [18]. Humans synthesize oligosaccharides as free molecules or bound oligosaccharides to lipids as glycolipids and to proteins as glycoproteins. They are ubiquitous on cell membranes as surface antigens, cell receptors, and cell adhesins. With few exceptions, complex oligosaccharides consist of a lactose core linked to lacto-N-biose, referred to as type I, or to N-acetyllactosamine, referred to as type II, by β1-3 or β1-6 linkages. The oligosaccharides may be decorated with fucose or sialic acid side chains. They may be fucosylated at α1, 2, α1, 3, or α1, 4 positions or sialylated at α2, 3 or α2, 6 positions [20]. Human oligosaccharides are also found in various secretions including milk, saliva, tears, and mucus. Milk has the highest concentration of oligosaccharides among all secretions. Fucosylated oligosaccharides predominate in milk [12, 21, 22].

Milk from all species of mammals contains oligosaccharides in varying amounts and types. The predominance of the type I lacto-N-biose core found in human milk is unique among mammals including other primates that contain only type II or a predominance of type II oligosaccharides [23]. The predominance of type I oligosaccharides in human milk is matched to the nutritional needs of bifidobacteria [24].

**Milk oligosaccharides and bifidobacteria**

In contrast to simple oligosaccharides such as lactose, which are digested and absorbed in the small intestine, complex oligosaccharides are not digested by humans, but are digested primarily by bifidobacteria and secondarily by bacteroides. Bifidobacteria are uniquely capable of metabolizing every type of oligosaccharide in human milk. Bifidobacteria ferment the oligosaccharides and produce two types of short-chain fatty acids: acetate and lactate [25]. Acetate generated by bifidobacteria may be used by other gut microbiota to produce butyrate—perhaps the most important short-chain fatty acid in the intestine [24]. Short-chain fatty acids also create an acidic environment in the gut that protects against invasion by enteric pathogens. Unfortunately, the pH in the intestinal lumen of the breastfed infant has risen over the past 100 years [26]. The decline in intestinal acidity has been attributed to the reduction in an abundance of bifidobacteria and short-chain fatty-acid production [25]. The increased use of infant formula and the increase in the number of deliveries by cesarean section may have contributed to reduced colonization with bifidobacteria.

**Secretion of milk oligosaccharides**

Not all mothers are able to secrete oligosaccharides into milk. Eighty percent of Americans are secretors and 20% are not [27]. The percentage of secretors and non-secretors varies in different regions of the world. The percentage of non-secretors is 43% in Europe, 54% in the Middle East and North Africa, and 42%–45% in Asia [26]. The rate of non-secretors in sub-Saharan Africa is ~26%—a rate similar to that in Americans. The reason for regional difference in rates of secretors and non-secretors remains unknown; however, one could speculate that there is a selective advantage to regional differences based on diet and/or exposure to intestinal infectious agents that may alter gene expression. Fucosyl α1, 2 oligosaccharides comprise the majority of oligosaccharides in human milk [27, 28]. The ability to secrete fucosyl α1, 2 oligosaccharides depends on the presence of the fucosyl α1, 2 transferase (FUT2) gene (Figure 1). The gene is located on chromosome 19 [29]. More than 50 different single-nucleotide polymorphisms have been identified in the FUT2 gene [26]. A dozen FUT2 polymorphisms have been reported, with G428A (Trp143→Ter) identified as the major FUT2 nonfunctional mutation in the US population [30]. Interestingly, C428A mutation is rare in the Asian population. Asian non-secretors or low secretors often carry nonfunctional allele A385T (Ile129→Phe) [31]. Non-secretors typically are genetically homozygous for an enzyme-inactivating nonsense mutation at the FUT2 locus and lack α1, 2 fucosyl oligosaccharide in all secretions [30, 32]. The lack of FUT2 oligosaccharides in non-secretors has been associated with reduced bifidobacterium diversity, richness, and abundance in children and adults [33, 34].

**Infant vs adult strains of bifidobacterium**

There are more than 40 different species of bifidobacterium. Because several strains present in the human gut are diet- and/or age-dependent, infants who are breastfed tend to be colonized with *Bifidobacterium infantis*, *B. breve*, and *B. bifidum* strains [9, 24, 35, 36]. *Bifidobacterium infantis* is unique among all strains of bifidobacterium because it has the greatest capacity to metabolize the various types of oligosaccharides in human milk. It may represent upwards of 90% of the gut microbiome of breastfed infants in underdeveloped countries [33, 34, 37, 38]. However, in developed countries such as the USA, *B. breve* and *B. bifidum* are much more frequent than *B. infantis* [39]. The number of bifidobacterium colonizing the gut of infants on a milk-based diet declines dramatically when milk is discontinued as the primary nutrient [40]. *Bifidobacterium longum*, *B. adolescentis*, *B. animalis*, *B. catenulatum*, and *B. pseudocatenulatum*, which lack the ability to digest milk oligosaccharides, replace the infant strains when the milk-based diet ceases [13, 41–44]. The adult strains of bifidobacterium are capable of digesting oligosaccharides found in a variety of starches and plants [6]. *Bifidobacterium breve* appears to play a regulatory role in retaining the infant microbiome while inhibiting the appearance of an adult microbiota.
between 1 and 2 years of age [45]. Perhaps this is nature’s way of preserving a healthy gut milieu in young children. Among all bifidobacteria, B. bifidum is the only strain capable of metabolizing gut mucins, suggesting it has a role in adulthood [46, 47]. Retaining bifidobacteria in the gut may well play a role in the prevention of several systemic disorders including obesity, inflammatory bowel disease, diabetes, liver disease, atherosclerosis, and metabolic syndrome [8, 48].

Conclusions
Human milk is the ideal diet during infancy. Oligosaccharides in human milk play a pivotal role in establishing a healthy gut microbiome. Bifidobacterium, the pre-eminent member of the infant gut microbiota, requires fucosyl s1, 2 oligosaccharide as a nutrient and for short-chain fatty-acid production. Only mothers with the functional FUT2 genes are able to secrete fucosyl s1, 2 oligosaccharides into milk. Mothers lacking functional FUT2 genes produce milk deficient in fucosyl s1, 2 oligosaccharides; their breastfed infants are colonized with fewer numbers and a less diverse group of bifidobacterium. Breastfeeding in early life was associated with microbiota in Dutch children of school age [49]. Early-life gut microbiota has been shown to relate to the development of obesity in older Norwegian children [50]. However, neither study determined the secretor status of either mother or child. There must be advantages and disadvantages to being a secretor or non-secretor in different regions of the world and among different ethnic groups to account for the exiting differences in the rates of secretors and non-secretors.

Conflict of interest
None declared.

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