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Review

REVIEW

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, *bifidobacterium*, 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].

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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 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 αl, 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, G428A 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. catenultum*, and *B. pseudocatenultum*, 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

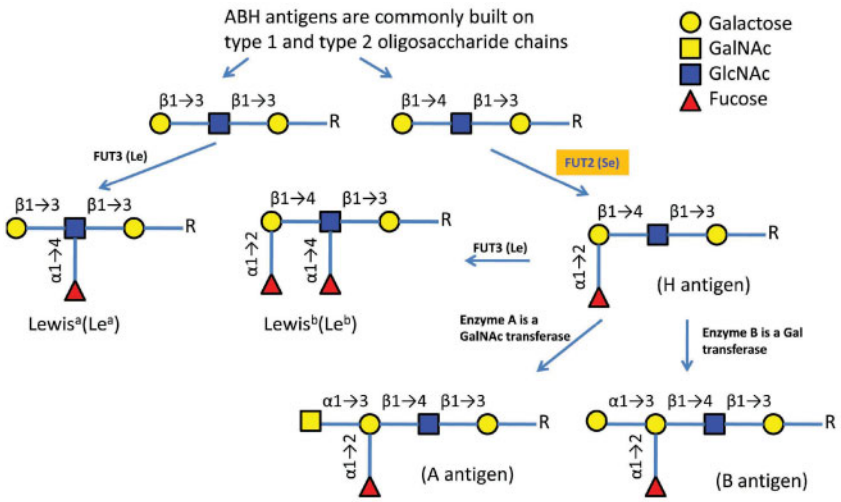

Figure 1. Role of the fucosyl αl, 2 transferase (*FUT2*) gene in the production of blood-group antigens. *FUT2*, the secretor (Se) gene, encodes fucosyl α1, 2 transferase, which adds a fucose α1, 2 connected to the galactose on the type 2 oligosaccharide chain at an early step of the ABH antigen synthesis. The immediate product of the fucosyl α1, 2 transferase is the H antigen, which can be further modified into antigen A by a GalNAc transferase or into antigen B by a Gal transferase. The H antigen can also be modified into Lewis^b antigen by another fucose transferase encoded by FUT3 (Le), α1, 4 fucosyltransferase. Lewis^a antigen is a product from the type 1 oligosaccharide chain modified by α1, 4 fucosyltransferase.

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 α1, 2 oligosaccharide as a nutrient and for short-chain fatty-acid production. Only mothers with the functional *FUT2* genes are able to secrete fucosyl α1, 2 oligosaccharides into milk. Mothers lacking functional *FUT2* genes produce milk deficient in fucosyl α1, 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.

References

1. Luk B, Veeraragavan S, Engevik M *et al.* Postnatal colonization with human "infant-type" bifidobacterium species alters behavior of adult gnotobiotic mice. *PLoS One* 2018;**13**:e0196510.
2. Carlson AL, Xia K, Azcarate-Peril MA *et al.* Infant gut microbiome associated with cognitive development. *Biol Psychiatry* 2018;**83**:148–59.
3. Schretter CE, Vielmetter J, Bartos I *et al.* A gut microbial factor modulates locomotor behaviour in Drosophila. *Nature* 2018;**563**:402–6.
4. Prince AL, Antony KM, Ma J *et al.* The microbiome and development: a mother's perspective. *Semin Reprod Med* 2014;**32**:14–22.
5. Stilling RM, Moloney GM, Ryan FJ *et al.* Social interaction-induced activation of RNA splicing in the amygdala of microbiome-deficient mice. *Elife* 2018;**7**.
6. Turroni F, Milani C, Duranti S *et al.* Bifidobacteria and the infant gut: an example of co-evolution and natural selection. *Cell Mol Life Sci* 2018;**75**:103–18.
7. Liu B, Newburg DS. Human milk glycoproteins protect infants against human pathogens. *Breastfeed Med* 2013;**8**:354–62.
8. Castanys-Munoz E, Martin MJ, Vazquez E. Building a beneficial microbiome from birth. *Adv Nutr* 2016;**7**:323–30.
9. Newburg DS, He Y. Neonatal gut microbiota and human milk glycans cooperate to attenuate infection and inflammation. *Clin Obstet Gynecol* 2015;**58**:814–26.
10. Mueller NT, Bakacs E, Combellick J *et al.* The infant microbiome development: mom matters. *Trends Mol Med* 2015;**21**:109–17.
11. Backhed F, Roswall J, Peng Y *et al.* Dynamics and stabilization of the human gut microbiome during the first year of life. *Cell Host Microbe* 2015;**17**:852.
12. Wang M, Li M, Wu S *et al.* Fecal microbiota composition of breast-fed infants is correlated with human milk oligosaccharides consumed. *J Pediatr Gastroenterol Nutr* 2015;**60**:825–33.
13. Hidalgo-Cantabrana C, Delgado S, Ruiz L *et al.* Bifidobacteria and their health-promoting effects. *Microbiol Spectr* 2017;**5**.
14. Tamburini S, Shen N, Wu HC *et al.* The microbiome in early life: implications for health outcomes. *Nat Med* 2016;**22**:713–22.
15. Yoshioka H, Iseki K, Fujita K. Development and differences of intestinal flora in the neonatal period in breast-fed and bottle-fed infants. *Pediatrics* 1983;**72**:317–21.

16. Section on Breastfeeding. Breastfeeding and the use of human milk. *Pediatrics* 2012;**129**:e827–41.
17. Centers for Disease Control and Prevention. *Breastfeeding Report Card*. Atlanta, Georgia: Centers for Disease Control and Prevention, 2018.
18. Bode L. The functional biology of human milk oligosaccharides. *Early Hum Dev* 2015;**91**:619–22.
19. Lammerts van Bueren A, Mulder M, Leeuwen SV *et al*. Prebiotic galactooligosaccharides activate mucin and pectic galactan utilization pathways in the human gut symbiont bacteroides thetaiotaomicron. *Sci Rep* 2017;**7**:40478.
20. Smilowitz JT, Lebrilla CB, Mills DA *et al*. Breast milk oligosaccharides: structure-function relationships in the neonate. *Annu Rev Nutr* 2014;**34**:143–69.
21. Totten SM, Zivkovic AM, Wu S *et al*. Comprehensive profiles of human milk oligosaccharides yield highly sensitive and specific markers for determining secretor status in lactating mothers. *J Proteome Res* 2012;**11**:6124–33.
22. Ninonuevo MR, Park Y, Yin H *et al*. A strategy for annotating the human milk glycome. *J Agric Food Chem* 2006;**54**:7471–80.
23. Urashima T, Asakuma S, Leo F *et al*. The predominance of type I oligosaccharides is a feature specific to human breast milk. *Adv Nutr* 2012;**3**:473S–82S.
24. Turroni F, Milani C, Duranti S *et al*. Glycan utilization and cross-feeding activities by bifidobacteria. *Trends Microbiol* 2018;**26**:339–50.
25. Henrick BM, Hutton AA, Palumbo MC *et al*. Elevated fecal pH indicates a profound change in the breastfed infant gut microbiome due to reduction of bifidobacterium over the past century. *mSphere* 2018;**3**.
26. Ferrer-Admetlla A, Sikora M, Laayouni H *et al*. A natural history of FUT2 polymorphism in humans. *Mol Biol Evol* 2009;**26**:1993–2003.
27. Newburg DS, Ruiz-Palacios GM, Altaye M *et al*. Innate protection conferred by fucosylated oligosaccharides of human milk against diarrhea in breastfed infants. *Glycobiology* 2004;**14**:253–63.
28. Kunz C, Meyer C, Collado MC *et al*. Influence of gestational age, secretor, and lewis blood group status on the oligosaccharide content of human milk. *J Pediatr Gastroenterol Nutr* 2017;**64**:789–98.
29. Reguigne-Arnould I, Couillin P, Mollicone R *et al*. Relative positions of two clusters of human alpha-L-fucosyltransferases in 19q (FUT1-FUT2) and 19p (FUT6-FUT3-FUT5) within the microsatellite genetic map of chromosome 19. *Cytogenet Cell Genet* 1995;**71**:158–62.
30. Kelly RJ, Rouquier S, Giorgi D *et al*. Sequence and expression of a candidate for the human secretor blood group alpha(1, 2)fucosyltransferase gene (FUT2). Homozygosity for an enzyme-inactivating nonsense mutation commonly correlates with the non-secretor phenotype. *J Biol Chem* 1995;**270**:4640–9.
31. Pang H, Koda Y, Soejima M *et al*. Polymorphism of the human ABO-Secretor locus (FUT2) in four populations in Asia: indication of distinct Asian subpopulations. *Ann Hum Genet* 2001;**65**:429–37.
32. Koda Y, Soejima M, Liu Y *et al*. Molecular basis for secretor type alpha(1, 2)-fucosyltransferase gene deficiency in a Japanese population: a fusion gene generated by unequal crossover responsible for the enzyme deficiency. *Am J Hum Genet* 1996;**59**:343–50.
33. Yatsunenko T, Rey FE, Manary MJ *et al*. Human gut microbiome viewed across age and geography. *Nature* 2012;**486**:222–7.
34. Underwood MA, German JB, Lebrilla CB *et al*. Bifidobacterium longum subspecies infantis: champion colonizer of the infant gut. *Pediatr Res* 2015;**77**:229–35.
35. Avershina E, Storro O, Oien T *et al*. Bifidobacterial succession and correlation networks in a large unselected cohort of mothers and their children. *Appl Environ Microbiol* 2013;**79**:497–507.
36. Zivkovic AM, German JB, Lebrilla CB *et al*. Human milk glycobiome and its impact on the infant gastrointestinal microbiota. *Proc Natl Acad Sci USA* 2011;**108(Suppl 1)**:4653–8.
37. Garrido D, Ruiz-Moyano S, Mills DA. Release and utilization of N-acetyl-D-glucosamine from human milk oligosaccharides by Bifidobacterium longum subsp. infantis. *Anaerobe* 2012;**18**:430–5.
38. Garrido D, Dallas DC, Mills DA. Consumption of human milk glycoconjugates by infant-associated bifidobacteria: mechanisms and implications. *Microbiology* 2013;**159**:649–64.
39. Fanaro S, Chierici R, Guerrini P *et al*. Intestinal microflora in early infancy: composition and development. *Acta Paediatr Suppl* 2003;**91**:48–55.
40. Khonsari S, Suganthy M, Burczynska B *et al*. A comparative study of bifidobacteria in human babies and adults. *Biosci Microbiota Food Health* 2016;**35**:97–103.
41. Marcobal A, Sonnenburg JL. Human milk oligosaccharide consumption by intestinal microbiota. *Clin Microbiol Infect* 2012;**18(Suppl 4)**:12–5.
42. Arboleya S, Watkins C, Stanton C *et al*. Gut bifidobacteria populations in human health and aging. *Front Microbiol* 2016;**7**:1204.
43. Turroni F, Ribbera A, Foroni E *et al*. Human gut microbiota and bifidobacteria: from composition to functionality. *Antonie Van Leeuwenhoek* 2008;**94**:35–50.
44. Turroni F, Berry D, Ventura M. Editorial: bifidobacteria and their role in the human gut microbiota. *Front Microbiol* 2016;**7**:2148.
45. Avershina E, Lundgard K, Sekelja M *et al*. Transition from infant- to adult-like gut microbiota. *Environ Microbiol* 2016;**18**:2226–36.
46. Ruiz L, Delgado S, Ruas-Madiedo P *et al*. Proteinaceous molecules mediating bifidobacterium-host interactions. *Front Microbiol* 2016;**7**:1193.
47. Thomson P, Medina DA, Garrido D. Human milk oligosaccharides and infant gut bifidobacteria: molecular strategies for their utilization. *Food Microbiol* 2018;**75**:37–46.
48. McGovern DP, Jones MR, Taylor KD *et al*. Fucosyltransferase 2 (FUT2) non-secretor status is associated with Crohn's disease. *Hum Mol Genet* 2010;**19**:3468–76.
49. Zhong H, Penders J, Shi Z *et al*. Impact of early events and lifestyle on the gut microbiota and metabolic phenotypes in young school-age children. *Microbiome* 2019;**7**:2.
50. Stanislawski MA, Dabelea D, Wagner BD *et al*. Gut microbiota in the first 2 years of life and the association with body mass index at age 12 in a Norwegian Birth Cohort. *MBio* 2018;**9**.