



# HHS Public Access

Author manuscript

*Curr Opin Clin Nutr Metab Care*. Author manuscript; available in PMC 2021 January 13.

Published in final edited form as:

*Curr Opin Clin Nutr Metab Care*. 2020 July ; 23(4): 277–281. doi:10.1097/MCO.0000000000000658.

## Carbohydrate composition in breast milk and its effect on infant health

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### Abstract

**Purpose of review**—This narrative review presents the current state of available evidence regarding the role of breast milk carbohydrates on infant outcomes, with a primary focus on growth and body composition.

**Recent findings**—To date, there is a paucity of available data that exists in this realm. The current literature focuses on the role of two carbohydrate fractions in breast milk, and their relationships with infant outcomes in the first six months of life: oligosaccharides and fructose. A small but growing body of research indicates robust associations of both oligosaccharides and fructose in breast milk with infant weight and length, as well as bone, fat, and lean mass. There is also emerging evidence to support the role of these same carbohydrate fractions in breast milk in infant cognitive development.

**Summary**—The present state of the science suggests that oligosaccharides and fructose in breast milk play a role in infant growth and body composition and introduces intriguing associations of these two carbohydrate fractions with infant cognitive development as well.

### Keywords

breast milk; fructose; human milk oligosaccharides

## INTRODUCTION

'The World Health Organization recommends mothers worldwide to exclusively breastfeed infants for the child's first six months to achieve optimal growth, development and health. Thereafter, they should be given nutritious complementary foods and continue breastfeeding up to the age of two years or beyond.' Such declarative statements are universal in the public

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Conflicts of interest

There are no conflicts of interest.

health domain and guide governmental policies adopted by medical and health organizations. Yet, there is a lack of appreciation for what little is known about the composition of breast milk and its interindividual variation. To date, breast milk composition has been shown to be influenced by maternal BMI/metabolic health, age, diet, and infant sex, with environmental and behavioral factors also playing a role. The limited data on this most important aspect of infant nutrition has not gone unnoticed. In January 2020, the Food and Nutrition Board of the National Academies of Sciences, Engineering, and Medicine held a workshop entitled, 'Nutrition During Pregnancy and Lactation: Exploring New Evidence,' which featured recent, albeit limited, strides made in this effort. Of particular interest, and the impetus for this narrative review, was the agenda highlighting advances in our understanding of the role of carbohydrate composition in breast milk.

In this narrative review, we summarize the known relationships of carbohydrate constituents in breast milk to early infant health in two major sections. The first section addresses determinants of breast milk carbohydrates, including the role of maternal diet, obesity status, and genetic factors. The second section addresses whether variation in the concentration and compositional profile of breast milk carbohydrates are associated with infant growth and development. In this regard, most studies have focused on infant weight and body composition as outcomes, but there are several newer studies examining their association with infant cognitive development as well. Given the state of the science, we focus on oligosaccharides and fructose in breast milk, as there is compelling new evidence of the effects of these carbohydrate derivatives on early infant outcomes.

### **Determinants of breast milk carbohydrates**

Mature human milk contains approximately 7% carbohydrate, with the majority being lactose. However, there is emerging evidence that additional carbohydrate fractions play a significant role in determining early infant health. These include oligosaccharides, a family of structurally diverse unconjugated glycans with one or more residues that dictate their distinct function, as well as fructose, a constituent of added sugar that has become ubiquitous in the food supply and is found in breast milk [1■,2]. It follows that concentrations of these carbohydrates vary across women and over the course of lactation because of several factors.

### **Maternal diet**

Maternal diet plays a part in determining the composition of breast milk, with the micronutrient and fat content of breast milk appearing to be most modifiable by diet. In contrast, the macronutrient content of breast milk is fairly uniform between women, although it changes by stage of nursing and over the course of lactation. However, there is renewed interest in the influence of maternal diet on the carbohydrate composition of breast milk because of the ubiquity of added sugar in the current food environment.

The present-day pervasiveness of added sugar, namely, high-fructose corn syrup (HFCS), could introduce additional targets that have not been considered or explored before in breast milk and, until recently, were thought to be absent in breast milk. Berger *et al.* [1■] was one of the first to examine the influence of maternal added sugar during lactation on breast milk

lactose, glucose, and fructose concentrations. A cohort of exclusively breastfeeding mothers ( $n=41$ ) were randomized in a crossover design to consume a commercially available sugar-sweetened beverage (Coca Cola) or control beverage (Diet Rite). The sugar-sweetened beverage contained 65 g of added sugar in the form of HFCS, whereas the control beverage contained only artificial sweeteners. After a baseline sample of breast milk was collected, mothers consumed the assigned beverage and pumped one complete breast expression hourly for six consecutive hours (360min). The key finding from this work was the sugar-sweetened beverage had no effect on lactose or glucose concentrations, but significantly increased fructose concentrations in breast milk. This study presents three salient points: time to peak fructose concentration was 3h (180 min;  $9.4\pm 1.9\mu\text{g/ml}$ ); fructose concentration remained significantly above baseline up to 5h after intake (300 min;  $P<0.01$ ); and the mean area under the curve for fructose was significantly higher in response to the sugar-sweetened beverage versus control beverage ( $14.7\pm 1.2$  versus  $-2.60\pm 1.2\mu\text{g/ml}\times 360$  min;  $P<0.01$ ).

Several key questions remain to be answered to better understand the role of maternal diet on fructose in breast milk: Does maternal consumption of added sugar, mainly in the form of HFCS versus natural fructose (as fruits and vegetables) contribute to fructose concentration in breast milk to the same extent? Does the timing of exposure to fructose through breast milk have a differential effect on early infant health? These and similar questions are currently unresolved.

### Maternal obesity

The metabolic state of the mother (e.g., BMI, diabetes) also has a significant influence on the composition of her breast milk. Maternal obesity has recently been reported to affect breast milk inflammation, insulin, and leptin levels; however, there is little to no evidence of its influence on glucose or smaller carbohydrate derivatives [3-5]. For example, a study of exclusively breastfeeding mother-infant dyads ( $n=37$ ) revealed that there was an interaction between maternal prepregnancy BMI and infant sex on concentrations of insulin in breast milk at 6 months ( $P=0.03$ ) [5]. For mothers classified as obese and nursing female infants, concentrations of insulin were 229% higher than those classified as normal weight with female infants, and 179% higher than those classified as obese with male infants [5]. A key finding from this work and others, however, was that maternal weight status was not associated with concentrations of glucose in breast milk [5,6]. This warrants attention, as it suggests that the glucose concentration in breast milk is tightly regulated by insulin and it is stable even in the presence of obesity and other metabolic conditions (e.g., diabetes).

More recently, the influence of maternal obesity on the carbohydrate composition of breast milk has been examined with more advanced analytical methods, for example, metabolomics. In a cohort of exclusively breastfeeding mother-infant dyads ( $n=35$ ), maternal prepregnancy BMI was associated with 10 metabolites in breast milk at one month [7]. Of these 10 metabolites, 30% were carbohydrates in the form of oligosaccharides: lacto-*N*-fucopentose 1 (LNFPI) and 2'-fucosyllactose (2'FL) were lower and LNFPII and LNFPIII were higher in mothers classified as overweight/obese versus normal weight (all  $P 0.05$ ). Moreover, maternal prepregnancy BMI was associated with 20 metabolites in breast milk at six months, of which 40% were carbohydrates in various forms (i.e.,

monosaccharides sugar alcohols): these were also higher among mothers classified as overweight/obese versus normal weight (all  $P < 0.05$ ) [7]. Overall, studies to date have shown that maternal weight status does alter small carbohydrates in breast milk but does not affect concentrations of glucose.

### Genetic determinants

There is a growing body of evidence showing breast milk composition is affected by genetic factors, with the greatest impact on oligosaccharides. The profile of oligosaccharides in breast milk is largely determined by maternal blood antigen 'secretor status,' which is genetically determined. Secretors possess the secretor (Se) gene, which encodes for the enzyme 2-fucosyltransferase (FUT2) and nonsecretors possess the Lewis (Le) gene, which encodes for the enzyme  $\alpha 1-3/4$ -fucosyltransferase (FUT3) [8]. It follows that secretor mothers who produce the enzyme FUT2 tend to have a higher abundance of fucosylated oligosaccharides (e.g., LNFPI and 2'FL) in their milk than nonsecretor mothers [8]. What is still unknown is whether this genetic determinant affects the abundance of oligosaccharides to such an extent that it alters early infant outcomes.

## A ROLE FOR BREAST MILK CARBOHYDRATES ON INFANT HEALTH

We acknowledge that the aim of this narrative review is to describe the current state of the science, yet there is a paucity of large well-controlled studies that examine the contribution of the carbohydrate fractions in breast milk on early infant outcomes. What is available, however, are a number of relatively small studies that report associations of the carbohydrate composition of breast milk in relation to infant weight and body composition. Moreover, there is emerging evidence on the carbohydrate composition of breast milk in association with infant neurodevelopment.

### Infant weight and body composition

There is limited data investigating the role of the carbohydrate composition in breast milk in relation to somatic growth, with the existing studies conflicted. Earlier studies have examined lactose and glucose concentrations in relation to infant weight and body composition [5,9]. More recent research explores associations of oligosaccharides with somatic growth outcomes [9,11]. Alderete *et al.* [10] conducted one of the first studies in mother-infant dyads ( $n=25$ ). Mothers completed a breast milk expression at 1 and 6 months, which were analyzed for oligosaccharides using high-pressure liquid chromatography (HPLC). Infants were measured for weight and length, as well-body composition (i.e., fat and lean mass) using dual-energy X-ray absorptiometry (DXA). The key finding from this work was that individual oligosaccharides were differentially associated with infant weight and body composition over the course of lactation. For example, an incremental increase in oligosaccharide LNFPI was associated with a 0.40-kg and a 1.11-kg lower infant weight at one and six months, respectively ( $P=0.03$ ); however, LNFPI was associated with lower infant fat and lean mass at six months only. Moreover, concentrations of disialyl-lacto-*N*-tetraose, LNFPII, and fucosyl-disialyl-lacto-*N*-hexaose were associated with higher infant fat mass and percentage fat, respectively, at six months only, and concentrations of lacto-*N*-neotetraose (LNnT) were associated with lower percentage fat at six months only [10].

In a more recent study, Larsson *et al.* [11] determined whether oligosaccharide composition in breast milk was associated with infant growth velocity and change in body composition. Mothers completed a breast milk expression at five months, which was analyzed for oligosaccharides using HPLC. Infants were measured for weight and length, as well as fat and lean mass using bioelectrical impedance [11]. The main finding from this work was that oligosaccharide 2'FL was associated with a higher weight velocity from 0 to five months, and a higher fat mass index (FMI) at five months ( $P=0.02$ ) in infants of secretor mothers. In addition, oligosaccharide LNnT was associated with a lower weight velocity from 0 to five months ( $P<0.01$ ), and a lower FMI at five months ( $P=0.03$ ) in infants of both secretor and nonsecretor mothers. This is in contrast to findings from a randomized controlled trial [12]. In this study, Puccio *et al.* [12] assigned infants to a cow's milk-based formula with oligosaccharides 2'FL and LNnT ( $n=88$ ) versus control ( $n=87$ ) from birth to six months. There were no differences in weight gain between treatment and control groups [mean difference (95% CI) treatment versus control:  $-0.30$  ( $-1.94, 1.34$ ) g/day]. To summarize, it is evident that oligosaccharides in breast milk have differential effects on infant somatic growth/body composition, but more work is required for a better understanding of their role in early infant health.

Although there have been strides in recent research on oligosaccharides, a less established area of interest is focused on associations of fructose in breast milk with somatic growth outcomes. In animals, fructose has been shown to influence weight and fat mass through several mechanisms. Fructose is known to interfere in the expression of hormones that regulate appetite, in favor of caloric consumption. Fructose also increases concentrations of oxidative stress markers and inflammatory mediators that infiltrate adipose tissue and exacerbate its expansion. What is unknown is how fructose metabolism affects early infant growth via breast milk exposure. In contrast to adults, infants do not have a developed gastrointestinal tract that is equipped to process fructose; for instance, infants lack the GLUT5 transporter, and GLUT5 expression is dramatically stimulated with early introduction of fructose. Because fructose is not a natural constituent of breast milk but can be introduced through maternal diet, inadvertent exposure to fructose may be detrimental to early growth and may have long-lasting metabolic consequences, though more needs to be learned.

To date, one study has examined associations of fructose in breast milk with infant weight and body composition. Goran *et al.* conducted a prospective design in 25 mother-infant dyads [2]. Mothers completed a breast milk expression at 1 and six months, which were analyzed for lactose, glucose, and fructose using liquid chromatography-mass spectrometry. Infants were measured for weight and length, as well as bone and body composition using DXA at both 1 and 6 months. The main finding from this work was that fructose in breast milk was the only carbohydrate associated with infant growth outcomes: with every  $1\mu\text{ml}$  increase in fructose, there was a 257-g increase in weight ( $P=0.02$ ), 170 g increase in lean mass ( $P=0.01$ ), 131 g increase in fat mass ( $P=0.05$ ), and 5 g increase in bone mineral content ( $P=0.03$ ). It remains unclear whether the relationships observed will have a meaningful impact on the development of obesity later in life.

## Infant cognitive development

The influence of carbohydrates in breast milk extends beyond somatic growth outcomes and into neurodevelopmental outcomes. Of the individual constituents in breast milk that support brain development, carbohydrates are of major importance, particularly with regard to oligosaccharides. In animals, oligosaccharides have been shown to influence brain function through several mechanisms: sialylated oligosaccharides contribute sialic acid to gangliosides for brain signaling, and a greater abundance of sialylated gangliosides enhances learning and memory [11]; and sialylated and fucosylated oligosaccharides act as prebiotics in the gut microbiome to support fermentation products for brain signaling, and a greater abundance of these same gut microbes enhances cognitive performance.

There is ample evidence that links oligosaccharides to cognitive development in animals, but a lack of data in humans exist. Berger *et al.* [13] were the first to address this gap in a cohort of mother–infant pairs ( $n=50$ ). In this prospective study, mothers completed a breast milk expression at one and six months, which were analyzed for the nineteen most abundant oligosaccharides. Infants were tested with the Bayley-III Scale of Cognitive Development at 24 months, which determined sensorimotor integration, concept formation, attention, habituation, and memory skills. Results revealed that exposure to a higher concentration of a single oligosaccharide, 2'FL, at 1 month predicted higher cognitive development scores in infants at 24 months ( $B=0.59$ ,  $P<0.01$ ). In contrast, there was no association of 2' at six months with cognitive development in infants ( $B=0.30$ ,  $P>0.05$ ) [13]. To summarize, this research suggests that earlier exposure to oligosaccharide 2'FL through breast milk may augment infant cognitive development during a critical window of brain development. What is still unknown is whether this beneficial effect endures as infants reach school-age and beyond.

In addition to the benefits of carbohydrates in breast milk on infant brain development, there is also interest in derivatives that may be detrimental. One that warrants attention is fructose. In animals, fructose has been shown to influence brain function through several mechanisms: fructose induces oxidative stress and increases concentrations of advanced glycation end products in the frontal cortex [14]; fructose interferes in actions of neurotrophins that regulate brain maturation [14]; and fructose increases concentrations of inflammatory mediators in the hippocampus [15]. Moreover, studies in children have shown that exposure to added sugar *in utero* was inversely associated with academic performance in mid-childhood [16]. However, no studies have examined exposure to fructose during lactation. Because fructose is detectable in breast milk and alters the areas of the brain that foster learning and memory, there is a need for more research that explores its implications in infants.

## CONCLUSION

To date, there is a paucity of studies that have examined the role of breast milk carbohydrates on infant growth/body composition. The current body of evidence suggests there may be an important role of both specific oligosaccharides, including 2'FL, and fructose in breast milk on growth/body composition in the first six months of life. Perhaps



most intriguing are studies that found an association of oligosaccharide concentrations with neurodevelopmental outcomes in the first 24 months, although these are far from conclusive.

## Acknowledgments

Financial support and sponsorship

D.A.F. and E.W.D. are supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under award number R01HD080444. P.K.B. is supported by the Eunice Kennedy Shriver National Institute of Child Health & Human Development of the National Institutes of Health under Award Number K99HD098288. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■ ■ of outstanding interest

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**KEY POINTS**

- Interest in understanding the composition of breast milk is garnering much enthusiasm, with the identification of carbohydrate derivatives outside that of lactose demonstrating a powerful influence on early infant health.
- Although the carbohydrate composition of breast milk was once assumed to be relatively stable, recently published work reports that breast milk fructose and oligosaccharide composition are impacted by maternal metabolic health and diet.
- There is limited data on the carbohydrate composition of breast milk in relation to infant growth. There is, however, emerging evidence that individual oligosaccharides and fructose have differential associations with infant weight and body composition in the first six months of life.
- There is exciting and emergent evidence that the carbohydrate composition in breast milk influences infant cognitive development. Although individual oligosaccharides may be beneficial, fructose appears to be detrimental to areas of the brain that foster learning and memory.