Clinical Benefits of Milk Fat Globule Membranes for Infants and Children

Olle Hernell, MD, PhD[1], Niklas Timby, MD, PhD[1], Magnus Domellöf, MD[1], and Bo Lönnerdal, PhD[2]

The milk fat globule membrane (MFGM) in breast milk contains many bioactive components. Infant formulas traditionally have been devoid of the MFGM fraction, but dairy technology now has made the addition of bovine MFGM technically feasible. We identified 6 double-blinded randomized controlled trials exploring the effects of MFGM supplementation on the diets of infants or children. Results suggest that supplementation is safe and indicate positive effects on both neurodevelopment and defense against infections. MFGM supplementation of infant formula may narrow the gap in cognitive performance and infection rates between breastfed and formula-fed infants. Because of the small number of studies and the heterogeneity of interventions, more high-quality double-blinded randomized controlled trials are needed, with well characterized and clearly defined MFGM fractions, before firm conclusions on the effects of MFGM supplementation on the health and development of infants can be drawn. *(J Pediatr 2016;173S:S60-5)*.

Observational studies have shown that early nutrition influences short- and long-term health of the infant. Formula-fed infants have, compared with breastfed infants, accelerated early weight gain,[1] higher incidence of infections during the first year of life,[2] lower cognitive scores,[3] and higher risk of overweight, obesity,[4] type 2 diabetes,[5] and unfavorable blood lipids[6] in adult life. Differences in the composition between infant formulas and human milk explain part of the observed differences in performance. Formula-fed infants have higher protein and energy intakes[7] and lower intakes of several biologically active factors present in human milk. Some of these factors are present in the milk fat globule membrane (MFGM).

Composition of the MFGM

The lactating mammary gland packages and releases lipids by a unique mechanism. In the cytoplasm of the epithelial cells, droplets of triacylglycerol are surrounded by a coating consisting of a phospholipid/cholesterol monolayer with incorporated proteins. These lipid droplets are secreted from the cells by fusion with the apical plasma membrane or by exocytosis over the apical plasma membrane, after being surrounded by secretory vesicles. This gives the lipid droplet in the lumen a triple phospholipid layer membrane, which consists of the coating monolayer and the phospholipid/cholesterol bilayer with proteins and glycoproteins derived from the plasma membrane or secretory vesicle (**Figure**). The proteins are located in different layers within the membranes, with the carbohydrates of the glycoproteins directed outward on the hydrophilic surface of the lipid droplet. The membrane surrounding the secreted fat droplets is called the MFGM. The lipid:protein weight of the MFGM is ~1:1.[8,9]

The lipid fraction of the MFGM is rich in phospholipids and cholesterol. Phospholipids make up 30% of the total lipid weight of the MFGM. Sphingomyelin, phosphatidylcholine, and phosphatidylethanolamine make up ~30% each of the total phospholipid content in MFGM.[8]

Biological Effects of Single Components of the MFGM

Choline is a highly methylated compound and a precursor for the biosynthesis of the membrane constituents, phosphatidylcholine, sphingomyelin, and choline plasmalogens, as well as the neurotransmitter acetylcholine. In foods, choline exists both unesterified and esterified as phosphocholine, glycerophosphocholine, phosphatidylcholine, and sphingomyelin. Choline metabolism is closely related to folate metabolism and choline is, like folate, essential for the development of the nervous system. The fetus and the neonate have high concentrations of choline in the blood and tissues. In mice, experimentally-inhibited uptake and metabolism of choline are associated with neural tube defects. In humans, women in the lowest quartile for daily choline intake have twice the risk of having a baby with a neural tube defect, compared with women in the highest quartile.[10] Low choline status in the first one-half of pregnancy was associated with poor

BFR	Breastfed reference
DBRCT	Double-blinded randomized controlled trial
EF	Experimental formula
MFGM	Milk fat globule membrane
MFGM-L	Lipid-rich MFGM
MFGM-P	Protein-rich MFGM
SF	Standard formula

From the [1]Department of Clinical Sciences, Umeå University, Umeå, Sweden; and [2]Department of Nutrition, University of California, Davis, CA

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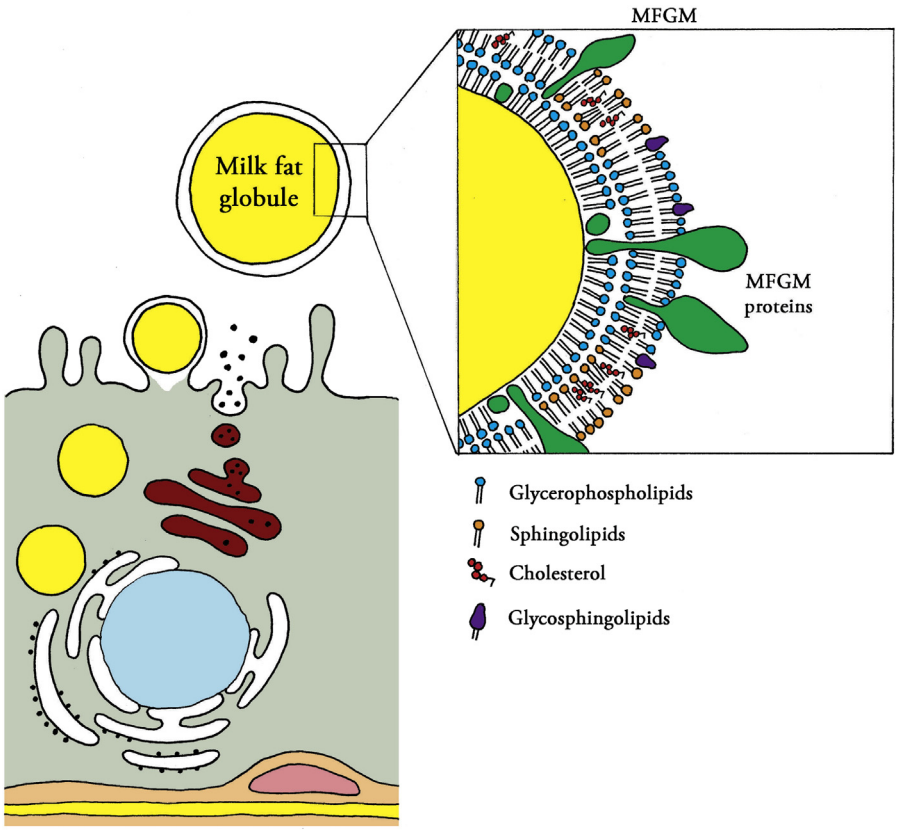

Figure. Schematic drawing of the release of the milk fat globule and composition of the MFGM. Illustration by Erik Domellöf.

cognitive development, measured with Bayley Scales of Infant Development, Third Edition, at 18 months.[11] In a rat model, supplementation with choline improved memory and learning.[12] In rats, there are 2 sensitive periods when oral choline supplementation provides positive effects on brain function: during neurogenesis and synaptogenesis. Extrapolating to humans, these periods would correspond to a period from in utero to 4 years of age.[13]

Sphingomyelin and its metabolites, ceramide, sphingosine, ceramide-1-P, and sphingosine-1-P, act as second messengers in cell signaling and have regulating effects on apoptosis, cell-cycle arrest, cell survival, cell proliferation, and inflammation.[14] In a rat model with experimentally-inhibited myelination of the nervous system, oral sphingomyelin increased myelination.[15] Oral sphingomyelin increases maturation of the intestine in rats.[16] Sphingomyelin also has been shown to have anticholesterolemic effects in rats by inhibiting intestinal absorption of cholesterol.[17,18] In a pilot study, 24 very low birth weight infants were randomized to receive, in addition to breast milk, sphingomyelin-fortified milk (sphingomyelin 20% of all phospholipids) or standard milk (sphingomyelin 13% of all phospholipids). In the neurodevelopmental follow-up between 6 and 18 months of age, infants in the sphingomyelin-fortified group had a more favorable outcome in the Behavior Rating Scale of the Bayley Scales of Infant and Toddler Development II, the Fagan test of infant intelligence, visual evoked potential latencies, and the free-play sustained attention test of Colombo.[19]

Gangliosides are sialic acid-containing glycosphingolipids known to be involved in neuronal growth, migration and maturation, neuritogenesis, synaptogenesis, and myelination.[20] There is growing evidence from different animal models supporting the importance of dietary gangliosides for optimal brain development during early life and optimal brain function throughout life.[21]

Cholesterol is essential and rate-limiting for the development of myelin in the central and peripheral nervous systems, and is involved in the differentiation of myelinating glial cells, in the process of myelin membrane biogenesis and in the functionality of mature myelin.[22] In elderly humans, total serum cholesterol concentration was positively correlated to cognitive function.[23] It is well known from early studies that serum cholesterol in infancy is higher in breastfed than formula-fed infants because of the higher cholesterol content in human milk.[24] The difference in serum cholesterol disappears in childhood,[25] and in adolescence and thereafter, previously breastfed infants have slightly lower serum cholesterol than their formula-fed counterparts.[26] Breastfeeding leads to downregulation of endogenous cholesterol synthesis via 3-hydroxy-3-methylglutaryl coenzyme A reductase.[27] In baboons, the lower cholesterol synthesis together with higher low-density lipoprotein receptor messenger