Supplementation of infant formula with bovine milk fat globule membranes.

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Abbreviations DBRCT, double-blinded randomized controlled trial; MFGM, milk fat globule membranes

Conflict of interest

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Abstract

Recent studies have shown that supplementation of infant formula with bovine milk fat globule membranes (MFGM) may significantly narrow the gap in health outcomes between formula-fed and breast-fed infants. In one study, feeding a formula supplemented with a lipid-rich MFGM concentrate between 2-6 months of age improved cognitive performance at 24 weeks of age. In another study, a formula supplemented with a protein-rich MFGM concentrate given between 2-6 months of age improved cognitive performance at 12 months of age, decreased infectious morbidity until 6 months of age and yielded serum cholesterol concentrations closer to those of breast-fed infants. A third study assessing safety of supplementing infant formula with a lipid-rich or a protein-rich MFGM concentrate found a non-inferior weight gain for both groups compared to a non-supplemented formula. In this study there was an increased risk of eczema in the protein-rich group but no serious adverse events.

Infant formulas with supplemental MFGM have been launched on the market in several countries. However, the evidence base must still be considered quite limited. Based on 3 randomized controlled trials, that are not comparable, the intervention seems safe, but there is not enough evidence for a general recommendation on which MFGM fraction and at what concentration to use as formula supplement for a given outcome.

Key words: MFGM, infant formula, neurodevelopment, cognition, infection, otitis, cholesterol
Introduction

A growing number of studies have reported health benefits from oral supplementation with bovine milk fat globule membranes (MFGM) to humans of different age groups, including infants (1). MFGM is the membrane surrounding the secreted fat droplets in milk. It is released by a unique mechanism in the mammary gland and is composed by a triple phospholipid and cholesterol layer with incorporated proteins and glycoproteins (2). A schematic drawing of fat release and MFGM composition is showed in Figure 1. The genes regulating MFGM synthesis are conserved across species indicating a functional benefit of the fraction in milk (3), even if the exact MFGM composition varies between species. Phospholipids make up 30% of the total milk lipid weight with sphingomyelins, phosphatidylcholines and phosphatidylethanolamines contributing approximately one third each (2). Almost all milk gangliosides are also located in the MFGM (4). The proteome of the human MFGM includes 191 different identified proteins including mucins, butyrophilin, lactoferrin and lactadherin (5). In a study on bovine MFGM-rich fractions, 244 proteins were identified in a whey protein concentrate and 133 in a buttermilk protein concentrate (6). MFGM is also rich in sialic acid as part of gangliosides (4) and glycosylated proteins.

Breast-fed infants have a higher intake of MFGM components compared to their formula-fed counterparts because traditionally, the MFGM fraction is discarded with the milk fat when this is replaced by vegetable oils as the fat source in infant formulas. Following advances in dairy technology, bovine MFGM concentrates are now commercially available and possible to use as a supplement to foods including infant formulas. MFGM has emerged as a complex factor that may explain some of the differences observed between breast-fed and formula-fed infants.
Current status of knowledge

Possible biological effects of MFGM components

The rationale for MFGM supplementation of infant formula is based on a growing number of studies showing health benefits of individual components of the MFGM, mostly in animal models, and a limited number of human studies on supplementation with different MFGM fractions.

Dietary gangliosides (7), sialic acid (8) and sphingomyelin (9) have been shown to be important for optimal brain development and function in different animal models. However, it should be noted that some of these models are disease models or models with inhibited de novo synthesis, which is far from supplementing a healthy infant. In a small study on premature infants with a birth weight < 1500 g, infants receiving formula with high sphingomyelin content (20 % vs. 13 % of all phospholipids in milk) to cover shortages of breast milk performed better at neurobehavioural follow-up between 6-18 months corrected age (10). Further, oral sphingomyelin increased maturation of the intestine in rats (11). Gangliosides have also been suggested to play an important role in the development of intestinal microbiota composition, gut immunity and, consequently, in the defense against infections (12). Other components of MFGM are also involved in the defense against infections, e.g. the glycoproteins butyrophilin, lactadherin and mucins (13, 14) all have anti-microbial effects, the lipid fraction of bovine MFGM has antiviral effect in vitro (15), and oligosaccharides inhibit binding of several bacteria (including pneumococci) to the mucosa. (14). Both lipid and protein components of MFGM have anticancer effects in vitro (13).

Dietary MFGM to adults and children after weaning

In human adults, most studies on dietary MFGM have focused on outcomes related to different risk factors for cardiovascular disease. Buttermilk consumption reduced serum cholesterol concentrations, primarily through inhibition of intestinal absorption of cholesterol (16) and decreased blood pressure and angiotensin-I-converting enzyme in moderately hypercholesterolemic adults (17). In contrast to milk fat without MFGM, milk fat enclosed by MFGM did not impair the lipoprotein profile in
overweight adults (18). Addition of an MFGM fraction to a high-saturated fat meal reduced the
cpostprandial insulineemic and inflammatory response in overweight and obese adults (19). Dietary
MFGM given to healthy adults have also been shown to have positive effects on gastrointestinal
symptoms from diarrheagenic E coli (20) and on muscle strength (21).

A few randomized studies on dietary MFGM supplementation of children after weaning have been
published. In a Peruvian study, an MFGM-enriched protein fraction given to healthy, primarily breast-
fed 6-11-mo-old infants during 6 months, decreased the longitudinal prevalence of diarrhea (3.84% vs.
4.37%, p<0.05) and the incidence of bloody diarrhea (OR =0.59, 95%CI 0.34-1.02, p=0.025) (22). In
contrast, a daily dose of milk powder supplemented with 2 g of a spray-dried ganglioside concentrate
given to infants 8-24 months of age for 12 weeks in India, did not affect diarrheal morbidity (23). In a
Belgian study, a phospholipid-rich MFGM concentrate given daily for 4 months to pre-school children
aged 2.5 to 6 years decreased behavioral problems and reduced days with fever during the intervention
period (24).

Supplementation with MFGM to term infants in early infancy

Three randomized controlled trials on MFGM supplementation to infant formula given to term infants
during the first half-year of life were identified in a search on PubMed performed 1st of September
2016 (Table 1).

In a double-blinded randomized controlled trial (DBRCT) in Indonesia, Gurnida et al evaluated the
impact on cognitive function of feeding a standard infant formula enriched with bovine milk
gangliosides, provided as a complex bovine milk lipid fraction (AnmumInfacare, Fonterra Cooperative
Group, Auckland, New Zealand) increasing the ganglioside content from 6 to 9 mg/L, compared to the
same formula without enrichment (control group), from 2 to 8 weeks (baseline) until 24 weeks of age
(25). A total of 70 healthy, term infants were randomized to either ganglioside supplemented (n=35;
29 completed the study) formula or control (n=35; 30 completed the study) formula. A breast-fed
reference group (n=40; 32 completed the study) was also recruited. Primary outcome was the Griffiths
Mental Developmental Scale at 24 weeks of age and secondary outcome was serum ganglioside concentrations. After adjustment for socioeconomic background variables, hand-eye coordination IQ (129.5 vs. 122.0, p=0.006), performance IQ (131.1 vs. 123.2, p<0.001) and general IQ (125.4 vs. 120.6, p=0.041) were higher in the ganglioside supplemented group compared to the control group, and the ganglioside supplemented group did not differ from the breast-fed reference group.

In a DBRCT in Umeå, Sweden, formula-fed healthy term infants were randomized to receive an experimental formula (n=80; 73 completed the study) supplemented with a protein-rich MFGM fraction (Lacprodan® MFGM-10, Arla Foods Ingredients, Viby, Denmark) or a control formula (n=80; 68 completed the study) from <2 to 6 months of age. The experimental formula had lower energy density (60 vs. 66 kcal/100 mL) and protein concentration (1.20 vs. 1.27 g/100 mL), and MFGM-proteins made up 4% (wt/wt) of the total protein content of the formula. A breast-fed reference group was also recruited (n=80; 72 fulfilled the study). Primary outcomes were weight at 6 months of age and psychological assessment using Bayley Scales of Infant Development, 3rd Ed (Bayley-III). The formula-fed infants regulated their ingested volumes by increasing meal size, resulting in no differences in energy intake, protein intake, blood urea nitrogen, s-insulin or growth, including body fat percent, up to 12 months of age (26, 27). At 12 months of age, the MFGM-supplemented group received higher scores (mean ± SD) in the cognitive domain of Bayley-III (105.8 ± 9.2) than the control group (101.8 ± 8.0, p=0.008) and did not differ from the breast-fed reference group (106.4 ± 9.5, p=0.73) (26). There were no observed differences in socioeconomic background factors between the MFGM-supplemented and control formula groups. During the intervention, the MFGM-supplemented group had a lower incidence of acute otitis media than the control group (1% vs. 9%, p=0.034), lower incidence and longitudinal prevalence of antipyretic use and lower concentrations of s-IgG against pneumococci after vaccination (28). During the intervention, the MFGM-supplemented group gradually reached higher serum cholesterol concentrations than the control group and did not differ from the breast-fed reference group at 6 months of age (29).

In a multicenter non-inferiority DBRCT on 199 (149 completed the intervention) healthy term infants, Billeaud et al evaluated safety of two infant formulas enriched with a lipid-rich (MFGM-L) or a
protein-rich (MFGM-P) bovine MFGM fraction, respectively (30). At 14 days of age, the infants were randomized to receive standard infant formula (control), standard formula enriched with MFGM-L ( Fonterra Co-operative Group Limited, Auckland, New Zealand), or standard formula enriched with MFGM-P ( Lacprodan® MFGM-10, Arla Foods Ingredients, Viby, Denmark) until 4 mo of age. Primary outcome, weight gain, was non-inferior in the MFGM-L and MFGM-P groups compared with the control group. Among secondary and exploratory outcomes, few between-group differences were observed. Adverse events and morbidity rates were similar across groups except for a higher rate of eczema in the MFGM-P group (13.9% vs. 1.4% in the MFGM-L group and 3.5% in the control group, p=0.001). However, the limited number of observations and the lack of a systematic eczema scoring system make this result uncertain. In the Swedish study, no increased risk of rash was observed (31).

Conclusions

Two DBRCTs on MFGM supplementation of infant formula have shown promising effects on neurodevelopment and one DBRCT on infectious morbidity. The findings are supported by known effects of individual components of MFGM on neurodevelopment and protection against infection, mostly based on in vitro and/or animal studies. Further, all three identified DBRCTs concluded that the intervention was safe. Even if the results are promising, the scientific base of knowledge must still be considered quite limited. One of the studies had a small number of study subjects (25), and the study population in the other study (26) was from a homogenous, highly educated population with high socio-economic standard. Extrapolations of the results to a general population worldwide must be made with caution. The studies were performed with different MFGM concentrates. Different concentrates have different composition and each product should be tested for efficacy and safety. It is important that more high-quality randomized controlled trials with formulas supplemented with different types and concentrations of bovine MFGM including those already used are performed and that results, positive or negative, are published to increase the scientific body of evidence. A
systematic scoring system should be included in future studies to assess the occurrence of eczema (32).

MFGM supplementation of infant formula may be an important step towards narrowing the gap between formula-fed and breast-fed infants regarding neurodevelopment, infectious diseases and cholesterol metabolism. Infant formulas supplemented with bovine MFGM have already been launched on several markets, but there is not enough evidence for a general recommendation for MFGM-supplementation of infant formula.

Acknowledgment

All authors have read and approved the final manuscript.
References

19. Demmer E, Van Loan MD, Rivera N, Rogers TS, Gertz ER, German JB, Smilowitz JT, Zivkovic AM. Addition of a dairy fraction rich in milk fat globule membrane to a high-


Figure legend

**Figure 1.** Schematic picture of the release of the milk fat globule and composition of the milk fat globule membrane. Illustration by Erik Domellöf. Reprinted from (1), with permission from Elsevier.
<table>
<thead>
<tr>
<th>Site</th>
<th>Number of infants in final analysis of MFGM-supplemented/control</th>
<th>Age at intervention</th>
<th>MFGM supplement</th>
<th>Primary outcome&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Secondary outcomes&lt;sup&gt;1&lt;/sup&gt;</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indonesia</td>
<td>29 / 30</td>
<td>&lt;8 wk – 6 months</td>
<td>Complex milk lipids (AnnumInfacare, Fonterra Cooperative Group Auckland, New Zealand)</td>
<td>Higher general IQ, hand and eye coordination IQ and performance IQ on Griffith scale at 24 weeks.</td>
<td>Higher serum gangliosides GM3 and GD3.</td>
<td>(25)</td>
</tr>
<tr>
<td>Sweden</td>
<td>73 / 68</td>
<td>&lt;2 mo – 6 months</td>
<td>Lacprodan MFGM-10 (Arla Foods Ingredients, Viby, Denmark)</td>
<td>Higher cognitive score on Bayley-III at 12 months.</td>
<td>Lower incidence of otitis media. Higher serum cholesterol.</td>
<td>(26, 28, 29)</td>
</tr>
<tr>
<td>France and Italy</td>
<td>47 (MFGM-L) + 52 (MFGM-P) / 45</td>
<td>14 days – 4 months</td>
<td>MFGM-L: Lipid rich MFGM fraction (Fonterra Cooperative Group Auckland, New Zealand). MFGM-P: Lacprodan MFGM-10 (Arla Foods Ingredients, Viby, Denmark)</td>
<td>Non-inferior weight gain for both groups up to 4 months.</td>
<td>Higher rate of eczema in the MFGM-P group.</td>
<td>(30)</td>
</tr>
</tbody>
</table>

<sup>1</sup> For MFGM-supplemented group(s) in relation to formula-fed control group. MFGM, milk fat globule membranes.