Role Medium-Chain Fatty Acids in the Lipid Metabolism of Infants

Tinglan Yuan\textsuperscript{1,4}, Lei Wang\textsuperscript{1}, Jun Jin\textsuperscript{1}, Lijuan Mi\textsuperscript{2}, Jinzhu Pang\textsuperscript{2}, Zhengdong Liu\textsuperscript{3}, Jinyan Gong\textsuperscript{4}, Cong Sun\textsuperscript{5}, Jufang Li\textsuperscript{2,*}, Wei Wei\textsuperscript{1,*}, Qingzhe Jin\textsuperscript{1} and Xingguo Wang\textsuperscript{1}

\textsuperscript{1}Collaborative Innovation Centre of Food Safety and Quality Control in Jiangsu Province, School of Food Science and Technology, Jiangnan University, Wuxi, China, \textsuperscript{2}Inner Mongolia Mengniu Dairy (Group) Co., Ltd., Beijing, China, \textsuperscript{3}Yashili International Group Co., Ltd., Guangzhou, China, \textsuperscript{4}Zhejiang Provincial Key Lab for Biological and Chemical Processing Technologies of Farm Product, School of Biological and Chemical Engineering, Zhejiang University of Science and Technology, Hangzhou, China, \textsuperscript{5}College of Food Science and Technology, Henan University of Technology, Zhengzhou, China

Human breastmilk, the ideal food for healthy infants, naturally contains a high concentration of medium-chain fatty acids (MCFAs, about 15% of total fatty acids). MCFAs are an important energy source for infants due to their unique digestive and metabolic properties. MCFAs are widely used in infant formulas, especially formulas for preterm infants. Recently, there has been a growing interest in the triglyceride structure of MCFAs in human milk, their metabolism, and their effects on infant health. This study summarized the MCFA composition and structure in both human milk and infant formula. Recent studies on the nutritional effects of MCFAs on infant gut microbiota have been reviewed. Special attention was given to the MCFA digestion and metabolism in the infants. This paper aims to provide insights into the optimization of formulations to fulfill infant nutritional requirements.

Keywords: medium-chain fatty acids, human milk fat, infant formula, lipid metabolism, medium-chain triacylglycerols

INTRODUCTION

Dietary nutrition is vital for the metabolic outcome and development of infants. Human milk is the optimal source of nutrition for infants. Fat is an important component of milk, supplying \(~50\%\) of energy for infants (1). Human milk fat contains approximately 50 kinds of fatty acids (FAs), mostly in the form of triacylglycerols (TAGs), which are more than 98\% of the fat (2). Human milk is a natural source of medium-chain fatty acids (MCFAs), comprising approximately 10–35\% of the total FAs (3), and half of the TAG molecules in human milk contain MCFAs (4). MCFAs have great importance for infants with an immature digestive system (5).

By definition, MCFAs generally refer to saturated FAs, with a chain length of 6–12 carbons, naturally occurring in some vegetable oils (coconut and palm kernel oils) and milk fat (5, 6). Typical medium-chain TAG (MCT) is mainly composed of caprylic acid (8:0) and capric acid (10:0).

Abbreviations: FA, fatty acids; LCFAs, long-chain fatty acids; MCFAs, medium-chain fatty acids; MCT, medium-chain triacylglycerol; MLCTs, medium- and long-chain triacylglycerols; TAGs, triacylglycerols.
In milk fat, MCFAs are generally regarded as saturated FAs, with a chain length of 8–14 (7–10). During lactation, the mammary epithelial cells are the primary site for de novo FA synthesis, and the presence of an acyl thioester-hydrolase limits FA synthesis to more than 16 (11, 12); therefore, the main FAs synthesized de novo in mammary glands, such as 8:0, 10:0, 12:0, and 14:0, are known as MCFAs on the basis of the source of milk FAs, which was adopted in this review.

MCFA-enriched oils, such as coconut oil and palm kernel oil or MCT, are often added to infant formulas as a source of MCFAs to facilitate fat absorption and the growth of infants, especially in formulas designed for low birth weight or preterm infants (13, 14). MCFAs are an important source of energy because their properties during the processes of digestion, absorption, and metabolism are different from those of long-chain fatty acids (LCFAs) (6, 15). It has been well documented that MCFAs are more easily absorbed and oxidized for energy than LCFAs since they are primarily absorbed directly to the liver via the portal vein and rapidly transferred independently of the carnitine shuttle system to the mitochondria (6). The addition of MCT to infant formula could facilitate better absorption of lipids (16). MCFAs also display antiviral and antibacterial activities and have a functional impact on the modulation of the gut microbiota during early infancy (17, 18), which is related to the maturation of the immune system and general health (19).

As an important energy source, the role of MCFAs in lipid metabolism in infants deserves more attention. However, a recent updated systematic review has concluded that an MCT formula did not improve preterm infant growth or have fewer adverse effects (20). Knowledge of human milk and infant formulas has greatly increased, which will help to understand better the health benefits of different diets. In this paper, we focus on the advances and controversies in the MCFA nutrition of infants. This work is intended to provide a holistic review of MCFAs, from structural characteristics to metabolic effects in infants.

**MEDIUM-CHAIN FATTY ACIDS IN HUMAN MILK AND INFANT FORMULAS**

Human milk fat was considered the reference standard of an infant formula. The MCFAs in human milk have been well studied as important saturated fatty acids, and their content was influenced by multiple factors (21). The MCFAs in an infant formula depend on the oil species supplied. The difference in MCFA between human milk and the infant formula was seldom studied as important saturated fatty acids, and their content was influenced by multiple factors (21). The MCFAs in an infant formula could facilitate better absorption of lipids (16). MCFAs also display antiviral and antibacterial activities and have a functional impact on the modulation of the gut microbiota during early infancy (17, 18), which is related to the maturation of the immune system and general health (19).

Medium-chain fatty acids (8:0–14:0) account for 7–23% of the total FAs in human milk, and 12:0 and 14:0 are predominant, accounting for approximately 5% and 6%, followed by 10:0 and 8:0 (Table 1). It was found that the MCFA composition of human milk changes throughout lactations, with a lower amount in colostrum than in transitional and mature milk (22–27), which may be attributed to the immature metabolism of the mammary gland or the biosynthetic capacity in early lactation (12). A pooled data analysis suggested that MCFAs are comparable between preterm and term milk (26). Besides physiological factors, maternal dietary, and sociodemographic and environmental factors are associated with the MCFA composition of human milk (21). It has been suggested that rich n-3 LCFAs or high-carbohydrate and low-fat diet could stimulate the synthesis of de novo FAs in the cytoplasm of the mammary glands (1, 11), resulting in a higher content of MCFAs in human milk (9, 28, 29). Actually, lower levels of MCFAs were found in the human milk of obese mothers (BMI of over 30) relative to the overweight group (BMI between 25 and 30), which may have been caused by the high fat intake (30). Additionally, when mothers or infants suffered cold-like symptoms, the proportions of 10:0 and 12:0 of FAs in human milk were significantly lower (10).

**Triacylglycerol Containing Medium-Chain Fatty Acids Composition of Human Milk Fat**

Medium-chain fatty acids account for a small portion of human milk; however, recent studies have shown that approximately half of the TAG molecule species in human milk contain at least one MCFA (31, 32). Table 1 shows the content of the TAGs, containing MCFAs (8:0–14:0) in human milk collected in four countries, summarized from eight publications (4, 24, 31–36). The content varies from 16.95% to 47.11% of total TAG. Among these TAGs, only a few TAGs composed of three MCFAs (0.80–1.13%) were detected. MCFAs are naturally present in human milk as medium- and long-chain triacylglycerols (MLCTs). Particularly, it was recognized that the MCFAs mainly existed together with 16:0 and 18 FAs (18:0, 18:1 or 18:2), such as 12:0/16:0/18:1 (LaPO), 12:0/18:1/18:2 (LaOL), and 12:0/18:1/18:1 (LaOO) (37).

**Comparison of Medium-Chain Fatty Acids in Human Milk Fat and Infant Formula Fat**

Human milk fat is well-known as the best nutrition for infants and is generally considered the reference standard for the development of an infant formula. Our group has recently analyzed the FA and TAG composition of 180 commercial infant formulas on the Chinese market (38, 39). As for MCFAs, we have found that almost all of the formulas contained higher amounts of 8:0 than mature human milk. Infant formulas supplied with coconut oil generally contained more 12:0 than human milk (38, 40).

The main TAGs containing MCFAs were 12:0/12:0/12:0 (LaLaLa) and 12:0/12:0/14:0 (LaLaM) in the plant oil-based infant formulas. Short- and medium-chain TAGs, such as 4:0/12:0/16:0 (BuLaP), 4:0/14:0/16:0 (BuMP), and 6:0/14:0/16:0 (CoMP), were predominant in the cow milk or goat milk-based infant formulas (39). These compounds are very different from those naturally present in human milk (37). The significant differences in TAG molecular species containing MCFAs between...
human milk and infant formulas should be given more attention in the future, as they could lead to altered lipid metabolism and physiological health status.

**ROLES OF MEDIUM-CHAIN FATTY ACIDS IN LIPID DIGESTION AND ABSORPTION**

**Gastric Digestion and Absorption**

The digestion of lipids begins in the stomach, where the FAs are released by gastric lipase, which is present from the 11th week of gestation and reaches adult activity levels at birth (41). It has been shown that the gastric hydrolysis of fat is higher in infants fed with human milk than those fed with a formula, including the MCT formula, although the 8:0 and 10:0 were less abundant in human milk (approximately 2%) than those in an infant formula (approximately 24%) (42, 43). Moreover, a crossover study showed that MCFAs in the MCT formula (42% MCT) and the LCT formula (7% MCT) fed to 12 preterm infants were hydrolyzed to the same extent (44), suggesting that MCT supplementation has no improvement on gastric lipolysis, possibly because of the stimulation of lipase secretion by LCFAs (44, 45). Still, short-chain FAs and MCFAs could be absorbed directly through the stomach wall and enter the portal vein, so even MCT molecules could be partially absorbed (44, 46), which provides infants with a readily available energy source.

**Intestinal Digestion and Absorption**

Ingested fat is digested and absorbed primarily in the small intestine, where TAGs are mainly hydrolyzed by pancreatic lipase to form the primary products 2-monooacylglycerol and free FAs (47). Subsequently, these products and bile salts form mixed micelles and reach the enterocytes, where they are absorbed, resynthesized as TAGs, and packaged as chylomicrons. Alternatively, short-chain FAs and MCFAs can leave the intestine and are directly and rapidly released into the portal circulation (Figure 1: 48).

With MCFAs being absorbed easier and faster than LCFAs, it is expected that adding MCTs to formulas would promote the higher absorption of fat (49). Some studies have significantly improved fat absorption by infants fed the MCT formula compared with the LCT formula (50–52). However, other studies have indicated that the fat absorption in infants was similar irrespective of the MCT levels (45, 53). Additionally, a lower fat absorption from formulas than human milk was reported to be common (54), which may be partly affected by the different structures of TAGs containing MCFAs (MLCT vs. MCT/LCT). Previous animal studies have demonstrated that structured lipids MLCT from esterification of MCT and fish oil had a higher lymphatic absorption than the mixture of MCT/LCT (55, 56). The differences in hydrolysis products and FAs released from different TAGs may influence the production of some hormones that control the secretion of pancreatic enzymes and lipid digestion, causing different digestive activities (57). Still, the exact mechanism is not fully understood.

**TABLE 1 | Content of MCFAs and TAGs containing MCFAs in human milk*.**

| Country/area          | Sample information             | MCFAs 8:0-14:0 | TAGs containing 8:0-14:0 | Ref. |
|-----------------------|--------------------------------|----------------|--------------------------|------|
| Wuxi, China           | Preterm milk, n = 30           | 9.30           | 29.16                    | (4)  |
|                       | Full-term milk, n = 30         | 8.70           | 29.88                    |      |
| Zhengzhou, China      | Mature milk, n = 30            | 11.26          | 40.09                    | (36) |
| Wuhan, China          | Mature milk, n = 30            | 8.51           | 31.32                    |      |
| Harbin, China         | Mature milk, n = 30            | 7.54           | 31.77                    |      |
| Wuxi, China           | Colostrum, n = 103             | 8.04           | 22.57                    | (22, 32) |
|                       | Transitional milk, n = 103      | 13.65          | 34.73                    |      |
|                       | Mature milk, n = 103           | 12.10          | 31.90                    |      |
| Beijing, China        | Colostrum, n = 126             | 7.43           | 16.95                    | (24) |
|                       | Mature milk, n = 40            | 10.32          | 22.54                    |      |
| Hubei, China          | Transitional milk, n = 9        | –              | 27.10                    | (33) |
| Sichuan, China        | Transitional milk, n = 8        | –              | 31.53                    |      |
| Beijing, China        | Transitional milk, n = 10       | –              | 28.29                    |      |
| Hubei, China          | Mature milk, n = 9              | –              | 47.11                    |      |
| Sichuan, China        | Mature milk, n = 8              | –              | 42.26                    |      |
| Beijing, China        | Mature milk, n = 10             | –              | 38.56                    |      |
| Beijing, China        | Mature milk, n = 10             | 8.00<sup>a</sup> | 31.51<sup>b</sup>        | (31) |
| Finland               | Mature milk, n = 10             | 13.27<sup>a</sup> | 40.54<sup>b</sup>        |      |
| Denmark               | Colostrum, n = 45              | 10.68          | 31.15                    | (35) |
|                       | Transitional milk, n = 45       | 18.17          | 46.20                    |      |
|                       | Mature milk, n = 45             | 23.12          | 40.35                    |      |
| Italy                 | Mature milk, n = 1              | 18.57<sup>a</sup> | 30.80                    | (34) |

*Data on human milk for infants < 12 months of age; the values were estimated on the basis of the mean weight percentage (wt%) of total TAGs, unless otherwise indicated.

<sup>a</sup> Indicated the information was not reported.  <sup>b</sup> Values were mole%.  <sup>c</sup> The TAGs less than 1% were not included. TAGs, triacylglycerols; MCFAs, medium-chain fatty acids.
MODULATION OF THE GUT MICROBIOTA AND INTESTINAL DEVELOPMENT

MCFAs as the intestinal energy sources can also improve the growth performance of infants by improving intestinal function. The protective effect of MCFA-containing MCTs on the intestinal barrier and gut health has been supported in suckling piglets as an in vivo mammalian neonate model (58, 59). Studies have demonstrated that MCFA-containing MCTs in milk, especially 8:0, 10:0, and 12:0, have antimicrobial effects against several bacteria, such as Clostridium, Salmonella, and Helicobacter pylori, which might enhance resistance against intestinal pathogens (17, 60, 61). A recent study has determined that dietary supplementation with MCTs reduced the colonization of Candida in preterm infants (62). Nevertheless, there are no reports of how the MLCT structure in human milk being different from an infant formula would impact the establishment of the microbiota or gut-associated function in infants.

LIPID METABOLISM OF MEDIUM-CHAIN FATTY ACIDS IN INFANTS

Oxidation Metabolism

The metabolic fate of MCFA is chiefly catabolism by the liver, where the major pathway for FAs is β-oxidation in mitochondria. LCFAs cross the mitochondrial membrane with the aid of carnitine, whereas MCFA can enter independent of the carnitine transport system and undergo preferential oxidation by the tricarboxylic acid cycle (6), and the oxidation is not subject to inhibition by malonyl CoA (Figure 1; 48). Thus, the rapid and almost complete oxidation of MCT has been suggested.

Nevertheless, there might be a limit to the amount of MCT being completely oxidized by preterm infants. For example, in infants fed a formula containing 40% fat as MCT, an average of no more than 47% of the administered 8:0 was oxidized (63). Furthermore, Whyte et al. (64) found no significant differences in the rate of energy expenditure and energy storage between the MCT formula and the LCT formula, which meant that MCT was not oxidized, and portions undergo the same metabolic fate as LCT. Additionally, infants fed a commercial formula might store up to 12% of the MCFAs (8:0–10:0) in subcutaneous fat (65). Hence, incorporating high-level MCT into a formula will not necessarily improve the neonate's ability to consume or metabolize energy (66).

Another consequence of MCFA (MLCT or MCT) being easily oxidized is the effects on body fat accumulation and obesity, which have been well demonstrated in animal and clinical trials (67–69). MCFA may enhance mitochondrial function, lipid oxidation, and thermogenesis by modulating cellular signaling and regulating key circulating metabolites and hormones (70).

In a rodent model, consumption of MCFA in early life has been shown to prevent excessive fat accumulation and insulin sensitivity in adulthood (71). While limited in infants, the evidence points to a positive impact of MCFA on obesity.

Acetyl CoA can also be converted into ketone bodies, such as acetoacetate, 3-hydroxybutyrate (β-HB), and acetone, in the liver.
mitochondria (Figure 1). Extrahepatic tissues, including the brain, can use ketone bodies as fuel. For newborns and older infants, ketones are an essential and important source of energy for the brain (72). MCFAs, in particular, are ketogenic for infants, ketones are an essential and important source of brain, can use ketone bodies as fuel. For newborns and older infants, ketosis may be more beneficial for lipid metabolism and development in infants. It was observed that the levels of plasma n-9 monounsaturated FA significantly.

### CONCLUSION AND FUTURE PERSPECTIVES

Milk fat is naturally rich in MCFAs, which are very important to the growth and development of infants. Although the consensus is that MCFAs have a unique advantage in absorption and metabolism in infants, the benefits of MCT on the growth performance of infants are not clearly shown in clinical trials. It is necessary to determine how the TAG structure of MCFAs influences lipid digestion and absorption and causes the observed outcome. Moreover, the effects of different MCFAs (e.g., 12:0 and 14:0) on lipid metabolism warrant further investigation. Additionally, the distinct metabolic effects on infants resulting from the differences in the composition of TAGs containing MCFAs between an infant formula and human milk have not been fully addressed. The molecular species of TAGs containing MCFAs in natural fats, their metabolic processing, and the potential health benefits for infants are of great interest. We present a summary of recent studies on MCFA composition in human milk and an appraisal of the function and roles of MCFAs on long-term metabolism in infants, which will be conducive to the development of infant formulas.

### AUTHOR CONTRIBUTIONS

WW and JL designed the review. TY wrote the original manuscript. WW, LW, JJ, LM, JP, ZL, JG, CS, QJ, and XW reviewed and edited the manuscript. All authors read, discussed, and agreed to the published version of the manuscript.

### FUNDING

This work was supported by the Science and Technology Program of Inner Mongolia “Study on maternal and infant nutrition in different regions and development of a new generation of infant dairy products,” and the Key Scientific and Technological project in Henan Province (No. 202102110288).

### REFERENCES

1. Jensen RG. Lipids in human milk. Lipids. (1999) 34:1243–71.
2. Liu Z, Rochfort S, Cocks B. Milk lipidomics: what we know and what we don’t. Prog Lipid Res. (2018) 71:70–85. doi: 10.1016/j.plipres.2018.06.002
3. Wei W, Jin Q, Wang X. Human milk fat substrates: past achievements and current trends. Prog Lipid Res. (2019) 74:69–86.
4. Yuan T, Wei W, Zhang X, Wang L, Dai X, Ren C, et al. Medium- and long-chain triacylglycerols composition in preterm and full-term human milk across different lactation stages. LWT Food Sci Technol. (2021) 142:110907.
5. Jensen RG. The lipids in human milk. Prog Lipid Res. (1996) 35:53–92.
6. Bach AC, Babayan VK. Medium-chain triglycerides: an update. Am J Clin Nutr. (1982) 36:950–62. doi: 10.1093/ajcn/36.5.950
7. Haddad I, Mozzon M, Frega NG. Trends in fatty acids positional distribution in human colostrum, transitional, and mature milk. Eur Food Res Technol. (2012) 235:325–32.
8. Granot E, Ishay-Gigi K, Malaach L, Fidel-Rimon O. Is there a difference in breast milk fatty acid composition of mothers of preterm and term infants? J Matern Fetal Neonatal Med. (2016) 29:832–5. doi: 10.3109/14767058.2015.1020785
9. Novak EM, Innis SM. Impact of maternal dietary n-3 and n-6 fatty acids on milk medium-chain fatty acids and the implications for neonatal liver metabolism. Endocrinol Metab. (2011) 301:E807–17. doi: 10.1152/appendo.00225.2011
10. Gardner AS, Rahman IA, Lai C, Hepworth A, Trengove N, Hartmann PE, et al. Changes in fatty acid composition of human milk in response to cold-like symptoms in the lactating mother and infant. Nutrients. (2017) 9:1034. doi: 10.3390/nu90901034
11. Hachey DL, Silber GH, Wong WW, Garza C. Human lactation II: endogenous fatty acid synthesis by the mammary gland. Pediatr Res. (1989) 25:63–8. doi: 10.1203/00006450-198901000-00015
12. Neville MC, Picciano MF. Regulation of milk lipid secretion and composition. Annu Rev Nutr. (1997) 17:159–84. doi: 10.1146/annurev.nutr.17.1.159
13. Tantibhedhyangkul P, Hashim SA. Medium-chain triglyceride feeding in premature infants: effects on fat and nitrogen absorption. Pediatrics. (1975) 55:359–70.
28. Nasser R, Stephen AM, Goh YK, Clandinin MT. The effect of a controlled medium chain triglycerides in body weight control: fact or fancy? J Lipid Res. (1996) 37:708–13.

29. Rocquelin G, Tapsoba S, Dop MC, Mbemba F, Traissac P, Martinprével Y. Human milk and microstructure characterization. J Pediatr Gastroenterol Nutr. (2010) 5:3.

30. Marín MC, Sanjurjo A, Rodrigo MA, de Alaniz MJT. Long-chain triglycerides in feeding the low-birth-weight infant. Pediatrics. (1996) 108:400–8.

31. Kallio H, Nylund M, Boström P, Björkman J, Miettinen M. Human milk resolution with an algorithmic novel electrospray ionization tandem mass spectrometry method. Food Chem. (2017) 233:551–60. doi: 10.1016/j.foodchem.2017.04.122

32. Yuan T, Qi C, Dai X, Xia Y, Sun C, Sun J, et al. Triacylglycerol composition of breast milk during different lactation stages. J Agric Food Chem. (2019) 67:2272–8. doi: 10.1021/acs.jafc.8b06554

33. Tu A, Ma Q, Bai H, Du Z. A comparative study of triacylglycerol composition in human milk during different lactation stages. J Dairy Sci. (2017) 100:4255–67. doi: 10.3168/jds.2016-11338

34. Gastaldi D, Medana C, Giancotti V, Aggini R, Dal Bello F, Biaocchi C. HPLC-APCI analysis of triacylglycerols in milk fat from different sources. Eur J Lipid Sci Technol. (2011) 113:197–207.

35. Zou XQ, Huang JH, Jin QZ, Guo Z, Liu YF, Cheong LZ, et al. Model for human milk fat substitute evaluation based on triacylglycerol composition profile. J Agric Food Chem. (2013) 61:167–75. doi: 10.1021/jf304094p

36. Chen Y, Zhou XH, Han B, Yu Z, Yi HX, Jiang SL, et al. Regional isomer and enantiomer analysis of primary triglycerides in human milk by silver ion and chiral HPLC atmospheric pressure chemical ionization-MS. J Dairy Sci. (2020) 103:7761–74. doi: 10.3168/jds.2019-17353

37. Yuan T, Zhang H, Wang X, Yu R, Zhou Q, Wei W, et al. Triacylglycerol containing medium-chain fatty acids (MCSA-TAG): the gap between human milk and infant formulas. Int Dairy J. (2019) 99:104545.

38. Sun C, Zou X, Yao Y, Jin J, Xiao Y, Huang J, et al. Evaluation of fatty acid composition in commercial infant formulas on the Chinese market: a comparative study based on fat source and stage. Int Dairy J. (2016) 63:42–51. doi: 10.1016/j.idairyj.2017.09.005

39. Sun C, Wei W, Zou X, Huang J, Jin Q, Wang X. Evaluation of triacylglycerol composition in commercial infant formulas on the Chinese market: a comparative study based on fat source and stage. Food Chem. (2018) 252:154–62. doi: 10.1016/j.foodchem.2018.01.072

40. Fabritius M, Linderborg KM, Tarvainen M, Kalpio M, Zhang Y, Yang B. Direct inlet negative ion chemical ionization tandem mass spectrometric analysis of triacylglycerol regioisomers in human milk and infant formulas. Food Chem. (2020) 328:126991. doi: 10.1016/j.foodchem.2020.126991

41. Bourlieu C, Ménard O, Bouzerzour K, Mandrali G, Macierzanka A, Mackie AR, et al. Specificity of infant digestive conditions: some clues for developing relevant in vitro models. Crit Rev Food Sci Nutr. (2014) 54:1427–57. doi: 10.1080/10408398.2011.640757

42. Armand M, Hamosh M, Mehta NR, Angelus PA, Philipott JR, Henderson TR, et al. Effect of human milk or formula on gastric function and fat digestion in the premature infant. Pediatr Res. (1996) 40:429–37. doi: 10.1203/00006450-199609000-00011

43. Roman C, Carriere F, Villeneuve P, Pina M, Millét V, Simeoni U, et al. Quantitative and qualitative study of gastric lipolysis in premature infants: do MCT-enriched infant formulas improve fat digestion? Pediatr Res. (2007) 61:83–8. doi: 10.1203/pdr.0b013e3180125bce

44. Hamosh M, Bittman J, Liao TH, Mehta NR, Buczek RJ, Wood DL, et al. Gastric lipolysis and fat absorption in preterm infants: effect of medium-chain triglyceride or long-chain triglyceride-containing formulas. Pediatrics. (1989) 83:86–92.

45. Hamosh M, Mehta NR, Fink CS, Coleman J, Hamosh P. Fat absorption in premature infants: medium-chain triglycerides and long-chain triglycerides are absorbed from formula at similar rates. J Pediatr Gastroenterol Nutr. (1991) 13:143–9.

46. Jensen RG, Jensen GL. Specialty lipids for infant nutrition. I. Milks and formulas. J Pediatr Gastroenterol Nutr. (1992) 15:232–45. doi: 10.1097/00000517-199210000-00002

47. Mattson HF, Wolpoff RA. The digestion and absorption of triglycerides. J Biol Chem. (1964) 239:2772–7.

48. Harvey RA, Ferrier DR. Lippincott's Illustrated Reviews: Biochemistry. Philadelphia, PA: Lippincott Williams & Wilkins (2011).

49. Guillot E, Lemarchal P, Phorraine T, Rerat A. Intestinal absorption of medium chain fatty acids: in vivo studies in pigs devoid of excocrine pancreatic secretion. Br J Nutr. (1994) 72:545–53. doi: 10.1017/S000711450000858

50. Huston RK, Reynolds JW, Jensen C, Buist NR. Nutrient and mineral retention and vitamin D absorption in low-birth-weight infants: effect of medium-chain triglycerides. Pediatrics. (1983) 72:44–8.

51. Roy CC, Ste-Marie M, Chartrand L, Weber A, Bard H, Doray B. Correction of the malabsorption of the preterm infant with a medium-chain triglyceride formula. J Pediatr. (1975) 87:446–50. doi: 10.1016/s0021-3460(75)80098-3

52. Okamoto E, Muttart CR, Zucker CL, Heird WC. Use of medium-chain triglycerides in feeding the low-birth-weight infant. Am J Dis Child. (1982) 135:428–31. doi: 10.1001/archpedi.1982.03970140046011
53. Wu PYK, Edmond J, Morrow J, Auestad N, Ponder D, Benson J. Gastrointestinal tolerance, fat absorption, plasma ketone and urinary dicarboxylic acid levels in low-birth-weight infants fed different amounts of medium-chain triglycerides in formula. J Pediatr Gastroenterol Nutr. (1993) 17:145–52. doi: 10.1097/00005176-199308000-00004

54. Imms SM. Dietary triacylglycerol structure and its role in infant nutrition. Adv Nutr. (2011) 2:275–83. doi: 10.3945/an.111.004488

55. Jensen G, McGarvey N, Taraszewski R, Wixson S, Seidner D, Pai T, et al. Lymphatic absorption of enterally fed structured triacylglycerol versus physical mix in a canine model. Am J Clin Nutr. (1994) 60:518–24. doi: 10.1093/ajcn/60.4.518

56. Too P, Lee T, Demichele SJ. Lymphatic absorption of structured triglycerides vs. physical mix in a rat model of fat malabsorption. Am J Physiol. (1999) 277:G333–40. doi: 10.1152/ajpgi.1999.277.2.G333

57. Borovicka J, Schweizer W, Mettraux C, Kreiss C, Remy B, Asal K, et al. Regulation of gastric and pancreatic lipase secretion by CCK and cholinergic mechanisms in humans. Am J Physiol. (1997) 273:G374–80. doi: 10.1152/ajpgi.1997.273.2.G374

58. Zentek J, Buchheit-Renko S, Ferrara F, Vahjen W, Van Kessel AG, Pieper R. Nutritional and physiological role of medium-chain triglycerides and medium-chain fatty acids in piglets. Anim Health Res Rev. (2011) 12:83–93. doi: 10.1017/S1466252311000089

59. De Keyser K, Dierick N, Kanto U, Hongsapak T, Buyens G, Kuterna L, et al. Storage of medium-chain triglycerides versus physical mix in a rat model of fat malabsorption. J Pediatr Gastroenterol Nutr. (2014) 60:518–24. doi: 10.1093/ajcn/64.2.152

60. Fischer CL, Drake DR, Dawson DV, Blanchette DR, Brodgen KA, Wertz PW. Antibacterial activity of sphingoid bases and fatty acids against gram-positive and gram-negative bacteria. Antimicrob Agents Ch. (2012) 56:1157–61. doi: 10.1128/AAC.05115-11

61. Sun CQ, O’Connor CJ, Roberton AM. Antibacterial actions of fatty acids and monoglycerides against Helicobacter pylori. FEMS Immunol Med Microbiol. (2003) 36:9–17. doi: 10.1016/S0928-8244(03)00008-7

62. Arsenault AB, Gunsalus KTW, Laforce-Nesbitt SS, Przystac L, DeAngelis EJ, Hurley ME, et al. Dietary supplementation with medium-chain triglycerides reduces candida gastrointestinal colonization in preterm infants. Pediatr Infect Dis J. (2019) 38:164–8. doi: 10.1097/INF.0000000000002042

63. Sulksers EJ, Lafeber HN, Sauer PJ. Quantitation of oxidation of medium-chain triglycerides in preterm infants. Pediatr Res. (1989) 26:294–7. doi: 10.1203/00006450-198910000-00003

64. Whyte RK, Campbell D, Stanhope R, Bayley HS, Sinclair JC. Energy balance in low birth weight infants fed formula of high or low medium-chain triglyceride content. J Pediatr. (1986) 108:964–71. doi: 10.1016/s0022-3476(86)80941-6

65. Sarada P, Lepage G, Boy C, Chessex P. Storage of medium-chain triglycerides in adipose tissue of orally fed infants. Am J Clin Nutr. (1987) 45:399–405. doi: 10.1093/ajcn/45.2.399

66. Boroom PR. Medium-chain triglycerides in formula for preterm neonates: implications for hepatic and extrahepatic metabolism. J Pediatr. (1992) 120:S139–45. doi: 10.1016/s0022-3476(05)12148-x

67. Lee YY, Tang TK, Chan ES, Phuah ET, Lai OM, Tan CP, et al. Medium chain triglyceride and medium-and long-chain triglyceride metabolism, production, health impacts and its applications – a review. Crit Rev Food Sci Nutr. (2021) 62:4149–85. doi: 10.1080/10408398.2021.1873729

68. Matualatupaw JC, Bohl M, Gregersen S, Hermansen K, Afman LA. Dietary medium-chain saturated fatty acids induce gene expression of energy metabolism-related pathways in adipose tissue of abdominally obese subjects. Int J Obes (Lond). (2017) 41:1348–54. doi: 10.1038/ijo.2017.120

69. Bueno NB, de Melo IV, Florencio TT, Sawaya AL. Dietary medium-chain triglycerides versus long-chain triglycerides for body composition in adults: systematic review and meta-analysis of randomized controlled trials. J Am Coll Nutr. (2015) 34:175–83. doi: 10.1080/07315724.2013.879844

70. Huang L, Gao L, Chen C. Role of medium-chain fatty acids in healthy metabolism: a clinical perspective. Trends Endocrinol Metab. (2021) 32:351–66. doi: 10.1016/j.ten.2021.03.002

71. van de Heijning BJM, Oosting A, Kegler D, van der Beek EM. An increased dietary supply of medium-chain fatty acids during early weaning in rodents prevents excessive fat accumulation in adulthood. Nutrients. (2017) 9:963. doi: 10.3390/nu9060963

72. Cunnane SC, Crawford MA. Energetic and nutritional constraints on infant brain development: implications for brain expansion during human evolution. J Hum Evol. (2014) 77:88–98. doi: 10.1016/j.jhevol.2014.05.001

73. Lucas A, Boyes S, Bloom SR, Aynsley-Green A. Metabolic and endocrine responses to a milk feed in six-day-old term infants: differences between breast and cow’s milk formula feeding. Acta Paediatr Scand. (1981) 70:195–200. doi: 10.1111/j.1651-2227.1981.tb05541.x

74. Chamma CM, Bargut TC, Mandarim-de-Lacerda CA, Aguiia MB. A rich medium-chain triacylglycerol diet benefits adiposity but has adverse effects on the markers of hepatic lipogenesis and beta-oxidation. Food Funct. (2017) 8:778–87. doi: 10.1039/c6fo01663d

75. Hwang SY, Nango H, Kawashima R. Influence of dietary medium- and long-chain triglycerides on fat deposition and lipogenic enzyme activities in rats. J Am Coll Nutr. (1993) 12:643–50. doi: 10.1080/07315724.1993.10718355

76. Sulksers EJ, Lafeber HN, Van Goudoever JB, Kalhan SC, Beaufreure B, Sauer PJ. Decreased glucose oxidation in preterm infants fed a formula containing medium-chain triglycerides. Pediatr Res. (1993) 33:101–5. doi: 10.1203/00006450-199302000-00002

77. Carnielli VP, Rossi K, Badon T, Gregori B, Verlato G, Orzalli A, et al. Medium-chain triglycerides in formulas for preterm infants: effect on plasma lipids, circulating concentrations of medium-chain fatty acids, and essential fatty acids. Am J Clin Nutr. (1996) 64:152–8. doi: 10.1093/ajcn/64.2.152

78. Billeaud C, Bouse-Vaysse C, Coudeleo L, Steenhout P, Jaeger J, Cruz-Hernandez C, et al. Effects on fatty acid metabolism of a new powdered human milk fortifier containing medium-chain triacylglycerols and docosahexaenoic acid in preterm infants. Nutrients. (2018) 10:690.

79. Wu GH, Zaniolo O, Schuster H, Schlotzer E, Pradelli L. Structured triglycerides versus physical mixtures of medium- and long-chain triglycerides for parenteral nutrition in surgical or critically ill adult patients: systematic review and meta-analysis. Clin Nutr. (2017) 36:150–61. doi: 10.1016/j.clnu.2016.01.004

80. Li C, Ni Q, Pei Y, Ren Y, Feng Y. Meta-analysis of the efficacy and safety of structured triglyceride lipid emulsions in parenteral nutrition therapy in China. Clin Nutr. (2019) 38:1524–35. doi: 10.1016/j.clnu.2018.07.013

Conflict of Interest: LM, JP, and JL were employed by Inner Mongolia Mengniu Dairy (Group) Co., Ltd. ZL was employed by Yashili International Group Co., Ltd. The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher’s Note: All claims expressed in this article are solely those of the authors and do not necessarily represent those of their affiliated organizations, or those of the publisher, the editors and the reviewers. Any product that may be evaluated in this article, or claim that may be made by its manufacturer, is not guaranteed or endorsed by the publisher.

Copyright © 2022 Yuan et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.