Medium Chain Triglycerides: Advantages and Possible Drawbacks


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Medium chain triglycerides (MCTs) are composed of a mixture of caproic acid (C6:0), 1–2%, caprylic acid (C8:0), 65–75%, capric acid (C10:0), 25–35%, and lauric acid (C12:0), 1–2%. These medium chain fatty acids (MCFA) have a lower melting point than the long chain fatty acids (16.7°C, 31.3°C, and 63.1°C for caprylic, capric, and palmitic acids, respectively) and are therefore liquid at room temperature. These fatty acids are much more soluble in water than are long chain fatty acids (68 mg per 100 ml versus 0.72 mg per 100 ml at 20°C for caprylic and palmitic acids, respectively). Solubility in biological fluids is further increased because of the highly ionized state at neutral pH of the medium chain fatty acids (1).

The metabolism of medium chain fatty acids varies greatly from that of long chain fatty acids. The former are released from triglycerides at higher rates by digestive enzymes: lingual (2), gastric (3), and pancreatic lipases (4). Contrary to long chain fatty acids, the medium chain fatty acids are absorbed directly through the gastric mucosa, a finding reported previously for suckling rats (5,6) and recently also for the preterm infant (7). Intestinal metabolism and transport into the circulation are also different, medium chain fatty acids being released into the portal circulation and thus being transported chiefly to the liver, in contrast to long chain fatty acids, which are re-esterified in the intestinal mucosa and packaged into chylomicrons prior to their release into the lymphatics and then into the systemic circulation (4,8). Because most of the ingested medium chain fatty acids reach the liver, they are metabolized within hepatocytes where they are rapidly oxidized giving rise to ketone bodies, a process facilitated by the ability of these fatty acids to cross the double mitochondrial membrane, a process that for medium chain fatty acids, unlike for long chain fatty acids, does not require the presence of carnitine (1). Indeed, the liver produces 10 times more CO₂ from a caprylic (C8:0) then from palmitic (C16:0) acid (1).

Thus medium chain fatty acids are mainly a rapid source of energy and contribute
only little to lipogenesis (9) although it was recently reported that medium chain fatty acids can be stored in adipose tissue of orally fed infants (10).

Our understanding of MCT metabolism is based largely on animal studies, where it was reported that, in the rat, overfeeding with MCT results in diminished weight gain, fat deposition, and fat cell size (11). In the human, oxygen consumption was 12% higher after a 400-kcal meal of MCT, as compared to an increment of only 4% after an isocaloric meal of long chain triglycerides (12). The mild ketosis prevailing in the breast-fed infant (13), attributed to the medium chain fatty acid (MCFA) content of human milk, can be duplicated in infants fed formulas containing MCFA (14). The preferential incorporation of ketone bodies into brain and lung lipids (15,16) in the neonatal period suggests that MCFA are important also as substrates for organ growth and not only as energy source.

Because of our interest in the composition of human milk fat, especially as related to length of gestation and lactation, as well as in fat digestion and absorption, we have conducted several studies relating to medium chain fatty acids and their function in the neonate. The questions we have asked were: (a) What initiates the synthesis of MCFA in the human mammary gland? (b) To what extent are MCFA released from triglyceride in the stomach of the newborn? (c) Are MCFA absorbed through the gastric mucosa of the newborn? (d) Is fat absorption in the newborn improved by feeding MCT-containing formulas? and (e) What is the fate of MCT oil fed to infants as a fortifier of premature formula or human milk?

MEDIUM CHAIN FATTY ACIDS IN HUMAN MILK

Our recent studies have shown that medium chain fatty acids are present in pre-partum mammary secretions (17). Furthermore, their concentration is higher in the milk secreted by mothers of preterm infants during the course of lactation than in the milk of mothers of full-term infants (18).

Medium chain fatty acids (C-16) of milk are synthesized within the mammary gland because only this tissue contains a specific enzyme, thioesterase II, that is able to terminate fatty acid synthesis at a lower carbon number, as compared to thioesterase I present in other tissues that terminates the aliphatic carbon chain at or above C16 (19,20). Because fatty acids C10:0 and 12:0 are present in much lower concentrations in prepartum mammary secretion (obtained between 70 days and 1 day before term delivery) than in colostrum of women who deliver very prematurely (at 26–30 weeks’ gestation) (Table 1), we wondered what might be the trigger for MCFA synthesis in the human mammary gland. Comparison of the MCFA concentration in colostrum of women who deliver after various length of gestation shows that parturition seems to be the trigger for MCFA synthesis, since prepartum secretions obtained close to full-term delivery had much lower MCFA concentrations. Taking the milk/plasma ratio as an indicator of fatty acid origin (i.e., a ratio close to 1 indicates uptake from the circulation, and thus of dietary or fat depot origin, while a ratio >2 would indicate synthesis within the mammary gland), it is obvious
TABLE 1. Medium chain fatty acid synthesis in the human mammary gland

<table>
<thead>
<tr>
<th>Specimen</th>
<th>N</th>
<th>C10:0 (%)</th>
<th>C12:0 (%)</th>
<th>C14:0 (%)</th>
<th>Fat (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prepartum secretion</td>
<td>12</td>
<td>0.10</td>
<td>1.70</td>
<td>4.90</td>
<td>1.20</td>
</tr>
</tbody>
</table>
| (1–70 days prepartum)

| Postpartum colostrum                          |    |           |           |           |            |
| Very preterm infants (26–30 weeks)           | 18 | 0.26      | 3.09      | 5.52      | 2.00       |
| Preterm infants (30–37 weeks)                | 26 | 0.31      | 3.14      | 5.87      | 1.80       |
| Full-term infants (38–42 weeks)              |  6 | 0.27      | 3.10      | 6.81      | 2.20       |

*a Fatty acids: C10:0, capric (decanoic); C12:0, lauric; C14:0, myristic.
*b Prepartum secretions obtained from women who delivered at full term.
*c Gestational age (weeks) of the infants delivered.

that MCFA synthesis is fully developed shortly after delivery, resulting in milk/plasma ratio of 16 for capric (C10:0), 17 for lauric (C12:0), and 4.3 for myristic (C14:0) acids (21) (Fig. 1).

The concentration of medium chain fatty acids in milk depends on the diet, being high in women who consume a diet rich in carbohydrates and low in fat (22–24).

While this diet is natural in many parts of the world, it was recently suggested that the concentration of MCFA in the milk of American women might be augmented by increasing the carbohydrate and reducing the fat content of their diet, a process called “in vivo lactoengineering” (25). Recent studies suggest that high parity (10 or more children) markedly lowers the fatty acid synthesizing ability of the human mammary gland (26).

TO WHAT EXTENT ARE MCFA RELEASED FROM TRIGLYCERIDES IN THE STOMACH OF THE NEWBORN?

Lingual and gastric lipases have higher affinity for medium chain fatty acids and for long chain polyunsaturated fatty acids than for saturated long chain fatty acids (2,3). This preferential pattern of triglyceride hydrolysis is apparent already in the 1-day-old rats. In this species, milk fat content is high (>10%) and analysis of gastric contents after milk ingestion shows high levels of medium chain and long chain polyunsaturated fatty acids released through the action of lingual lipase, the only preduodenal digestive lipase in the rat (27) (Fig. 2). A similar pattern of hydrolysis of human milk fat by lingual lipase is also evident (Fig. 3). In vitro incubation of human milk fat with partially purified lingual lipase leads to rapid release of C10:0 and C12:0 (within 10 minutes of incubation) while long chain unsaturated fatty acids are released at lower rates (maximal hydrolysis at 30 minutes). No measurable release of C14:0 and C16:0 fatty acids was evident during this incubation time (28).
ARE MEDIUM CHAIN FATTY ACIDS ABSORBED THROUGH THE GASTRIC MUCOSA OF THE NEWBORN?

The very low content of C8:0 in all lipid classes, including the free fatty acids from gastric contents of milk-fed rats, indicated that this fatty acid might be directly absorbed through the gastric mucosa of suckling rats (6). Indeed, in contrast to the loss of C8:0, the free fatty acids were enriched in C10:0 and C12:0, indicating that the gastric lipolytic process released primarily medium chain fatty acids from milk triglycerides and that C10:0 and C12:0 were not absorbed completely in the stomach. These initial studies in suckling rats were followed by studies in preterm infants (7). In a recent study in which we have examined gastric digestion of formulas containing predominantly long chain fatty acids or as much as 39% medium chain fatty acids, similar results were obtained. Caprylic and capric acids (C8:0 and C10:0, respectively) were reduced in gastric triglycerides as compared with formula triglyceride, indicating preferential hydrolysis. Whereas the triglycerides of the MCT formula contained 30% C8:0 and 12% C10:0, gastric triglycerides contained only 6% of each of these fatty acids. Similarly, the triglycerides of the LCT formula

FIG. 1. Fatty acid synthesis in the human mammary gland 2 days after full-term delivery. Milk:plasma fatty acid ratios. Plasma and milk lipids were analyzed by gas-liquid chromatography. Ratios in excess of 1:0 indicate synthesis within the mammary gland. From Spear ML, et al. (21).
FIG. 2. Hydrolysis of rat milk in the stomach of 1-day-old pups. The pups were weaned from their mothers for 1 h and were allowed to suckle for 30 min after returning to the mothers. At the end of this period the pups were sacrificed and gastric contents removed and extracted for fatty acid analysis by gas-liquid chromatography. Adapted from Bitman J, et al. (6).

contained 3.8% C8:0 and 3.1% C10:0, whereas gastric triglycerides contained only 0.8% and 1.7% of these fatty acids, respectively. The loss of these fatty acids from the triglycerides in the stomach did not result in an increase in the percentage of these fatty acids in the free fatty acids fraction. Since these measurements were made 15 min after starting the gavage feeding, when most of the lipid was still in the stomach (94% of the MCT fed and 100% of the LCT fed), the disappearance of C8:0 and to a lesser extent of C10:0 indicates that these fatty acids had left the stomach, probably by absorption through the gastric mucosa (7). This study, which is the first to indicate that medium chain fatty acids are absorbed in the stomach of

FIG. 3. Hydrolysis of human milk fat by lingual lipase. Human milk fat was incubated with partially purified lingual lipase and samples were taken for analysis of fatty acids by gas-liquid chromatography.
TABLE 2. Fat absorption and growth rate in preterm infants fed medium chain triglyceride or long chain triglyceride formula

<table>
<thead>
<tr>
<th>Formula</th>
<th>Dietary fat (g/kg/day)</th>
<th>Fat excretion (g/kg/day)</th>
<th>Fat absorption (%)</th>
<th>Weight (g/day)</th>
</tr>
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<tr>
<td>Medium chain triglycerides (n = 12)</td>
<td>6.04 ± 0.54 (4.18–8.38)</td>
<td>1.04 ± 0.24 (0.15–1.87)</td>
<td>84.63 ± 3.14 (60.21–97.05)</td>
<td>23.0 ± 1.50 (15.71–34.28)</td>
</tr>
<tr>
<td>Long chain triglycerides (n = 12)</td>
<td>5.88 ± 0.48 (3.63–7.60)</td>
<td>1.02 ± 0.26 (0.18–2.29)</td>
<td>82.81 ± 4.01 (49.34–97.50)</td>
<td>20.85 ± 1.80 (22.42–32.85)</td>
</tr>
</tbody>
</table>

* Data are means ± SEM and ranges (in parentheses). Fat excretion and absorption were determined during a 3-day balance study. Weight gain was determined during 1 week when infants were fed either medium chain or long chain triglyceride formula. Each infant was fed each formula for 1 week. Infants were randomly assigned to start with either formula. The 12 infants studied had a gestational age of 28.7 ± 0.50 weeks (range 26–32 weeks) and postnatal age of 6.08 ± 0.81 weeks (range 2.6–12.4 weeks). From Hamosh M, et al. (7).

the newborn infant, suggests that MCTs provide a readily available energy source that can be absorbed much more rapidly than the other energy sources available to the newborn.

IS FAT ABSORPTION IN THE NEWBORN IMPROVED BY FEEDING MCT-CONTAINING FORMULA?

Medium chain fatty acids are often used in the nutritional management of premature infants (29–31). Indeed, absorption of individual medium chain fatty acids was found to be higher than that of long chain fatty acids (32). However, despite this finding, recent reports suggest similar fat absorption in infants fed MCT- or LCT-containing formulas (33–35). We have investigated this question using two formulas that were identical, except for differences in the fat blend (Mead Johnson Enfamil containing 88.3 kcal per 100 ml, 4.4% fat, 2.65% protein, and 9.71% carbohydrate; the MCT formula contained 42% of C8:0 and C10:0, and the LCT formula contained 7% of C8:0 and C10:0. Seventy-two-hour fat balance studies were conducted on days 4–7 of each formula regimen. As can be seen from Table 2, in this study, in which each infant served as his or her own control (each formula being fed for 1 week), there was no difference in fat absorption or weight gain when preterm infants were fed either MCT or LCT formula. As can be seen in Fig. 4, there was much variation among infants in the extent of fat absorption. In nine of the 12 infants studied, fat absorption ranged from 85 to 97%. Thus, although C8:0 is rapidly absorbed from the stomach, medium chain triglycerides do not seem to improve fat absorption or weight gain in preterm infants.

WHAT IS THE FATE OF MCT OIL FED TO INFANTS AS A FORTIFIER OF PRETERM FORMULA?

Infant feeds are often supplemented with MCT oil (Mead Johnson Co.) to increase the caloric density. We wondered whether this supplement, which is not homoge-
Comparison of fat absorption in premature infants fed alternately medium chain (MCT) or long chain (LCT) formula. Numbers next to symbols designate individual infant numbers. From Hamosh M, et al. (7) with permission.

nized before feeding, might not be delivered in its entirety and some of the fat might be lost. As shown in Fig. 5, depending on the mode of feeding, as much as 16% of fat fed to the infant might adhere to the gavage feeding set when MCT oil is mixed with human milk prior to feeding (36). Analysis of the fatty acid composition of the residual fat showed that it was composed mainly (up to 84%) of MCFAs (C8:0 and C10:0), as compared to the fat residue in the unfortified milk feeding sets in which the fatty acid chain lengths were >C12:0 (36) (Fig. 6). Our study thus raises some concerns about the method of fortification of infant feeds, and suggests that the MCT oil be fed first followed by delivery of the feed through the feeding set. The very high loss of medium chain fatty acids indicates that the feeding sets might have special affinity for these fatty acids. Our recent studies show that the medium chain fatty acids in preterm formulas that contain high levels of this fat blend are not adhering

**TABLE 3. Characteristics of medium chain fatty acids**

- High solubility in water
- Rapid release from triglyceride by digestive lipases
- Absorption through the gastric mucosa
- Transport from the intestine to the liver as FFA in the portal circulation
- Carnitine independent passage into mitochondria for oxidation
- Ketogenic
- Low deposition in adipose tissue
- Thermogenic
FIG. 5. Amount of fat adhering to feeding sets during intermittent feeding of fortified fresh human milk. Data are percent (mean ± SEM) of total fat adhering to feeding sets during four feeding regimens: (1) unfortified human milk; (2) MCT oil delivered first, followed by milk; (3) MCT oil premixed with milk before gavage feeding; and (4) milk fortified with PM 60/40. Numbers in each bar represent number of experiments. From Mehta NR, et al. (36) with permission.

FIG. 6. Fatty acid composition of fat adhering to feeding sets during gavage feeding of fortified human milk in four feeding regimens: (1) unfortified human milk; (2) MCT oil delivered first, followed by milk; (3) MCT oil premixed with milk before gavage feeding; and (4) milk fortified with PM 60/40. C8:0 (octanoic acid) and C10:0 (decanoic acid), major components of MCT oil; C16:0 (palmitic acid) and C18:1 (oleic acid), major components of human milk fat. From Mehta NR, et al. (36) with permission.
to the gavage tubes (37), probably because of the efficient emulsification of fat during the formula preparation process.

CONCLUSION

Animal and human studies have shown that medium chain fatty acids might improve fat digestion and absorption, are a rapid energy source, and a good source of ketone bodies and are not deposited efficiently in fat depots, thus having a potential role in weight-reducing diets (Table 3, page 87). These advantages are, however, balanced by the lack of improvement in fat absorption as well as by the tendency of these fatty acids to be lost through adherence to feeding tubes. It is therefore advisable to prepare fat blends that contain 10–20% MCFA (concentrations found in human milk), and to provide MCFA as an integral part of infant formulas rather than as an oil supplement. Much additional research is needed to assess the function of these fatty acids in the nutrition of infants and children.

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DISCUSSION

Dr. Van Hoof: I had expected more about the possible drawbacks of MCT. These could result from the rapid metabolic oxidation of medium chain fatty acids (dumping syndrome) and
also from the fact that they are less completely \( \beta \)-oxidized in mitochondria and undergo \( \omega \)-oxidation followed by incomplete peroxisomal \( \beta \)-oxidation, with important dicarboxylic aciduria. This has been demonstrated by several authors in humans. The contribution of peroxisomes explains why MCT oxidation produces only 7.5–8 kcal/g instead of 9 kcal for long chain triglycerides. But it is the enhanced production of dicarboxylic acids that is probably the most important point. It is certainly not harmless in inherited metabolic disorders with dicarboxylic aciduria (e.g., glutaric aciduria type II), and one might speculate that the continuous administration of MCT would create a condition in which very long chain fatty acids could accumulate, as well as the precursors of bile acids, because of the competition of substrates for the limited capacity of peroxisomal \( \beta \)-oxidation. These drawbacks, of course, are not expected to occur in breast-fed infants, because human milk is not that rich in MCT, but could occur with some formulas in which all the fat is constituted of MCT.

Dr. Roe: I am intrigued by the possibility that C10 compounds might benefit from carnitine. The concentration in human breast milk is 50 \( \mu \)mol, and there is virtually no acylcarnitine in breast milk. It might have been interesting to supplement some of these children with carnitine at the same time that they were receiving the MCT. I wonder if perhaps carnitine might result in more efficient oxidation.

Dr. Saudubray: Did you measure dicarboxylic acids and blood ketones?

Dr. Hamosh: No. It is very well known that breast-fed infants have higher blood levels of ketone bodies, which are directly proportional to the amount of medium chain fatty acids in milk. The same has been found in infants who were fed MCT.

Dr. Odievere: You mentioned the existence of lingual and gastric lipase activity. Both lipase and lipoprotein lipase activities have been found in the milk. My first question concerns the relative importance of lipase activity in milk versus that in the digestive system. My second question concerns breast milk jaundice in newborns. It was shown a few years ago that an excess of fatty acids may inhibit the bilirubin conjugating system in the liver and also may displace the bilirubin from the albumin in the plasma. Do you think that giving MCT to newborns may increase the risk of unconjugated hyperbilirubinemia?

Dr. Hamosh: The two enzymes that are present in milk are lipoprotein lipase and bile salt stimulated lipase. Lipoprotein lipase cannot act in the digestive system for three reasons. It is very rapidly inactivated at low pH, and by low pH, I really mean a pH of 3–4, which is the pH of the empty stomach when the milk is ingested. The second reason is that the enzyme has an absolute dependence on apoprotein C2 which will not be present in the stomach but only in the blood. The third point is that the pH optimum of the enzyme is quite restricted to between 7.5 and 8.5, so it could not act in the stomach; and of course, it could not act in the intestine, where the pH is higher, because of the very disruptive environment of bile salts, which would inhibit the enzyme. Bile-salt-stimulated lipase will hydrolyze milk fat in the intestine, not in the stomach, because it has a high pH optimum of 8.5–9.5 and has an absolute dependence on bile salts. We have shown recently that bile-salt-stimulated lipase cannot initiate the digestion of milk fat because it cannot penetrate the milk fat globules, whereas lingual lipase and gastric lipase, being very hydrophobic, can penetrate the globules and can initiate hydrolysis. Therefore, the subsequent hydrolysis of milk fat by the milk lipase in the intestine is dependent on predigestion of the milk fat globules in the stomach.

The second question was about breast milk jaundice, which has been attributed to a number of causes: higher levels of free fatty acids in milk, lately the possibly higher activity of milk \( \beta \)-glucuronidase in breast-fed babies, and the possibility of higher lipoprotein lipase activity in milk. We have investigated this topic and published our results (1) a few years ago. We showed
that there is no difference relevant to neonatal jaundice in milk lipases or β-glucoronidase activities (1) or in the amount of milk fat (2).

Dr. Mowat: I wonder if you have any observations on the time course of development of lipase, both lingual and gastric, particularly in the more immature babies (i.e., around 24 weeks). I know that a few studies seem to start at 32 weeks. And I wonder if you have any information on what the activities of these enzymes were nearer the time of delivery.

Dr. Hamosh: We have extensive data which were published between 1981 and 1984. We measured enzyme activities starting at 25 weeks’ gestation. Activity is very high from 25 weeks’ gestation and there is only a slight increase after 35 weeks.

Dr. Saudubray: Do we know what are the regulatory mechanisms for the elongation of fatty acids? Is there a difference when fatty acid synthesis starts from a very short molecule, such as acetoacetyl-CoA, and when it starts from longer molecules, such as a C8, C10, or C12?

Dr. Mannaerts: Denis McGarry and Dan Foster, working in Dallas, perfused livers with [1-14C]octanoate and looked where the labeled carbon atom was localized in long chain fatty acids, in order to discriminate between elongation and β-oxidation of the labeled octanoate to acetyl-CoA, and the reutilization of this acetyl-CoA for fatty acid synthesis. I think they saw very little elongation of octanoate.

Dr. Hamosh: In general, preterm infants have to be given long chain polyunsaturated fatty acids because they lack the ability to elongate and desaturate fatty acids. We don’t know at what age they acquire this ability.

Dr. Saudubray: With propionic and methylmalonic acidopathies we have a good model of accumulation of propionyl-CoA, which is a very good primer for odd-numbered fatty acid synthesis.

Dr. Hobbs: We have a paradox here. In the peroxisomal diseases, where accumulation of very long chain fatty acids occurs, they must be avoided. Now we are told that the medium chain varieties may overload the peroxisomes. So we have two different ways of stressing peroxisomal patients. Do you know whether these have been studied to see if they could explain the heterogeneous expression?

Dr. Wanders: I think what Professor Van Hoof was telling us about the hypothesis that MCT and dicarboxylic acids give rise to overloading of the peroxisomal system is an attractive model. Nobody has looked at the very long chain fatty acid levels or bile acid intermediates in these patients. It is something we should do.

Dr. Van Hoof: I think that high doses of MCT need to be given to bring about a pathological accumulation of very long chain fatty acids and bile acid precursors, since MCT are widely used without clinical problems, at least according to the literature.

Dr. Hamosh: I think it would be safe when we speak about normal full-term infants, without any biochemical abnormalities, to adhere to the concentration of MCT in human milk, because after all, the human species has survived, for better or for worse, on breast milk for a long time, with a concentration of about 5-10% MCT.

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