Medium-chain triglycerides: an update[1,2]

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ABSTRACT A review of the literature on the medical and nutritional use of medium-chain triglycerides (MCTs) since 1970 is presented with additional discussions on the various modifications and applications of the MCTs in the synthesis of certain structured lipids. The metabolism of MCTs in the liver and extrahepatic tissues is discussed along with further documentation of the use of MCTs in malabsorption and hyperlipidemia cases. Recent applications of MCTs and modified MCTs in hyperalimentation, deficiency in the carnitine system, epilepsy, obesity, and other special areas of application are cited. The use of medium-chain monodiglycerides for dissolving cholesterol gallstones is presented. The contraindications for the use of MCTs in ketosis, acidosis, and cirrhosis are also discussed. Suggestions for use of MCTs in a variety of medical and nutritional applications are presented. *Am J Clin Nutr* 1982;36:950–962.

KEY WORDS Medium-chain triglycerides, long-chain triglycerides, medium-chain fatty acid (C6:0–C12:0), long-chain fatty acid (C14:0 and longer), medium-chain monodiglycerides (monodiglycerides of caprylic and capric acids)

Introduction

Medium-chain triglycerides (MCTs) were first introduced in 1950 for the treatment of disorders of lipid absorption. Since then a great deal has been learned about the metabolism and clinical use of MCTs and of their fatty acids.

Herein, we have tried to evaluate the current state of the art of MCTs emphasizing, particularly, what has been learned since 1970. References 1 to 4 supply earlier bibliographical information.

Physicochemical properties

MCTs are made up of a mixture of C6:0 (1 to 2%), C8:0 (65 to 75%), C10:0 (25 to 35%), and C12:0 (1 to 2%) medium-chain fatty acids (MCFAs) obtained by the hydrolysis of coconut oil followed by the fractionation of the fatty acids. The MCFAs are esterified with glycerol with or without a catalyst to form the triacylglycerols (5). The melting point of the MCFAs is much lower (C8:0, 16.7°C; C10:0, 31.3°C) than that of the long-chain fatty acids (LCFAs) (C16:0, 63.1°C). Thus MCFAs, but also medium-chain triacylglycerols, are liquid at room temperature. By virtue of their smaller molecular size MCFAs are relatively soluble in water: the water solubility at 20°C is 68 mg/100 ml for C8:0 versus 0.72 mg for C16:0. The fact that MCFAs are weak electrolytes and are highly ionized at neutral pH, increases even more their solubility in biological fluids. As we shall see, the greater water solubility and the smaller molecular size of the MCFAs have consequences in all levels of their metabolism.

Absorption and metabolism

Absorption

The molecular weight of MCTs is smaller than the molecular size of long-chain triglycerides (LCTs). This facilitates the action of pancreatic lipase. Consequently, MCTs are hydrolyzed both faster and more completely than LCTs. In the case of mixed triacylglycerols the MCFAs are liberated preferentially. Mott et al (6) showed that in man, MCTs did not produce any change in pancreatic secretion, whereas with LCTs, there was a significant overall increase.

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The products of MCTs hydrolysis are absorbed faster than those of LCTs, and as fast as glucose (7). Since their intraluminal hydrolysis is rapid and relatively complete, the MCTs—unlike LCTs— are absorbed mainly as free fatty acids, and only rarely as monodiacylglycerols (**Fig 1**). In cases where bile salts or pancreatic lipase deficiency or both occur (8), a large fraction of MCTs can be absorbed as triacylglycerols, whereas LCTs cannot be absorbed. In enterocytes, these MCTs are then hydrolyzed by an intestinal lipase.

In the mucosa, LCFA are converted into acyl-CoAs in the presence of an acyl-CoA synthetase. The acyl-CoAs are then incorporated into triacylglycerols, which are a major component of chylomicrons. Since this enzyme is specific for fatty acids with more than 12 carbon atoms, the MCFAs are not significantly incorporated into chylomicrons; therefore, MCFAs leave the intestine faster than the LCFAs. The tendency of fatty acids to be esterified is directly proportional to their ability to bind to fatty-acid-binding protein (9, 10). MCFAs are not easily bound to this protein and are not easily esterified, while LCFAs are easily bound to this protein and incorporated abundantly into lipids.

MCFAs follow the portal venous system (Fig 1), whereas LCFAs follow the lymphatic system. Thus, MCTs do not stimulate the flow of lymph, while LCTs stimulate it significantly. The LCFAs are transported as chylomicrons, which are insoluble particles. The MCFAs, however, are transported in the soluble form of fatty acids, bound to serum albumin. This bond between MCFAs and albumin, however, is not as easily formed as that between LCFAs and albumin (11).

Because MCFAs leave the intestinal mucosa by the portal venous system, they reach the liver more rapidly than the longer molecules. The latter move via the extrahepatic tissues, where they may be partially retained. Thus, MCFAs reach the liver in greater abundance than do exogenous LCFAs. The majority of the MCFAs is retained in the liver, and only a small amount appears in the peripheral blood for a short period of time.

When LCTs and MCTs are ingested simultaneously, the latter partially inhibit the absorption of the former. Nevertheless, the total number of calories absorbed in this sit-

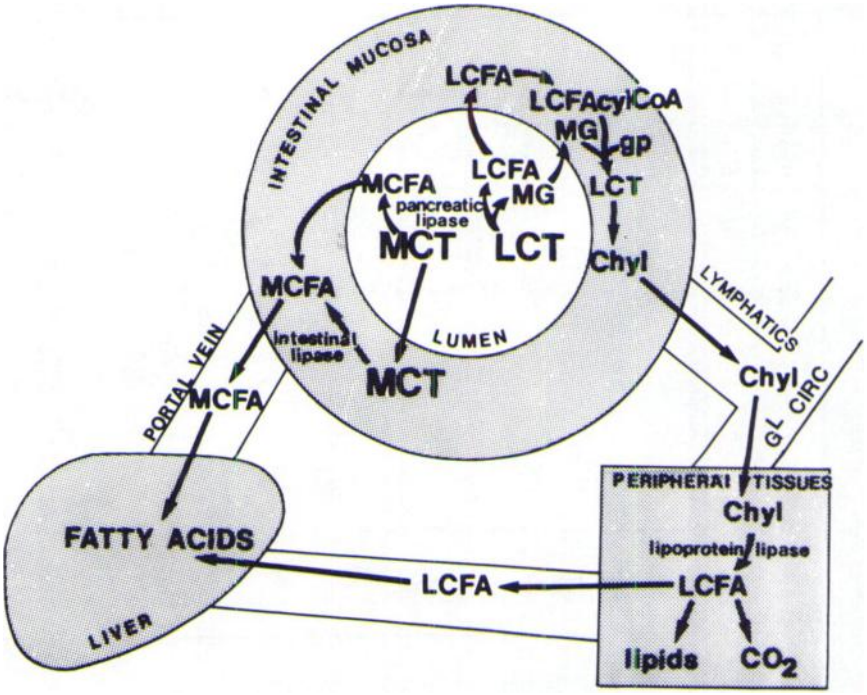

FIG. 1. Digestion, absorption, and transport of fats. *MG*, monoacylglycerol; *Chyl*, chylomicrons; gp, α-glycerophosphate; *G*' CIRC, general circulation.

uation is greater than the calories absorbed when either fat is ingested alone (12).

The mode of transport of MCFAs results in reduced sterol absorption (13). To be absorbed, sterols must be incorporated into micelles; and to be transported they must be bound to LCFAs, and incorporated into chylomicrons (14). These two processes do not take place with MCFAs and consequently the absorption of sterols is diminished.

The absorption of calcium (15) and magnesium appears to be enhanced when the diet contains MCTs, particularly in infants (16). The absorption of amino acids also appears to be improved (17, 18).

Hepatic metabolism

In the endoplasmic reticulum of the hepatocyte, the LCFAs are actively fixed on the fatty-acid-binding protein (9) and activated into acyl-CoAs under the influence of a long-chain-acyl-CoA synthetase (**Fig 2**). These acyl-CoAs then preferentially esterify α-glycerophosphate to give triacylglycerols and phospholipids; and esterify cholesterol, to give cholesterol esters. Because MCFAs do not bind easily to the fatty-acid-binding protein (19), and the acyl-CoA synthetase specific for these fatty acids is located in the mitochondrial matrix, MCFAs are almost never activated in the extramitochondrial space. Consequently, MCFAs are not significantly incorporated into the lipids synthesized by the hepatic tissue (20).

MCFAs cross the double mitochondrial membrane very rapidly and, unlike the LCFAs, they do not require the presence of carnitine (Fig 2) (21). In the mitochondrial matrix MCFAs are acylated by means of an octanoyl-CoA synthetase. In contrast, LCFAs or their acyl-CoA derivatives cannot cross the mitochondrial wall. In the presence of a carnitine palmityl transferase-I, LCFAs are transformed into acyl-carnitines that cross the membrane and regenerate long-chain-acyl-CoAs in the matrix, by the action of a carnitine palmityl transferase-II.

The mitochondrial acyl-CoAs, of whatever chain length, then undergo β-oxidation, with production of acetyl-CoA. In a healthy, well-nourished organism, relatively few LCFAs reach this stage at the same time, since these

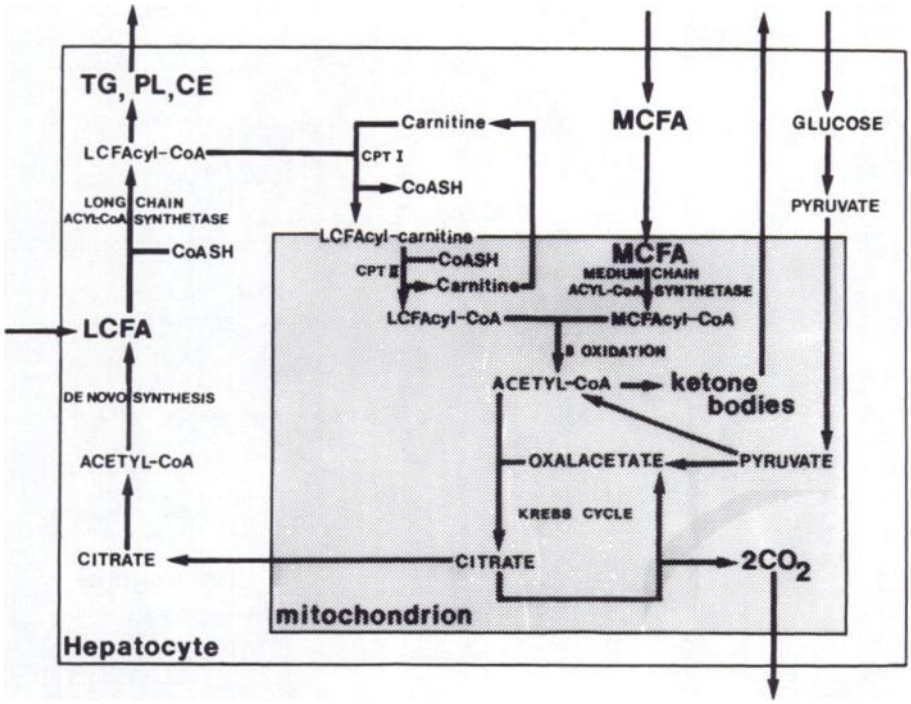

FIG. 2. Hepatic metabolism of fatty acids. *TG*, triacylglycerols; *PL*, phospholipids; *CE*, esterified cholesterol; CPT, carnitine palmityl transferase.

fatty acids tend to be incorporated into the lipids synthesized by the liver. The carnitine palmityl transferase complex is rather inactive under these conditions. The MCTs, however, are available and are rapidly oxidized. The result is an excess of acetyl-CoA (22), which then follows various metabolic pathways, both in the mitochondria (Krebs cycle, ketogenesis, elongation of fatty acids) and in the cytosol (de novo synthesis of fatty acids and cholesterol). During this accelerated β-oxidation of MCFAs, many hydrogen atoms are released, and thus the cell medium is noticeably reduced (22). Recently, it has been demonstrated that fatty acids can also undergo β-oxidation in the peroxisomes. But the amount of peroxisomal oxidation of MCFAs is negligible, because the key enzyme in this metabolic pathway, acyl-CoA oxidase, is not very active with acyl-CoAs that have fewer than 12 carbon atoms (23).

A fraction of the acetyl-CoA supplied enters into the Krebs cycle and is oxidized into CO_2. The liver produces about 10 times more CO_2 from C8:0 than from C16:0 (24); but the capacity of the Krebs cycle is limited (25). Furthermore, because of both the excess of acetyl-CoA produced from MCTs and the reduction in the cell medium, oxaloacetate will be in short supply (26) (Fig 2). A large part of the acetyl-CoA is then redirected toward the synthesis of ketone bodies.

MCTs are ketogenic (27, 28), much more so than LCTs. Wieland and Matschinsky (29) and McGarry and Foster (25, 30) found that the classic antiketogenic substances—fructose, glucose plus insulin, glycerol, and lactate—had little effect on the ketogenesis induced in the rat by octanoic acid. Freund and Weinsier (31), however, found that sucrose greatly decreased the amount of acetone in the air exhaled by subjects who had ingested MCTs. The simultaneous administration of MCTs and oxaloacetic acid donors noticeably reduces the production of ketone bodies from MCTs in the rat (26).

The mitochondria have a system that elongates fatty acids that have 12 or more carbon atoms. A small fraction of the acetyl-CoA produced during the oxidation of MCFAs serves to lengthen endogenous fatty acids. The relative importance of this metabolic pathway increases when LCTs are replaced by MCTs in the diet (32).

By complicated transfer mechanisms involving citrate and acetylcarnitine, acetyl-CoA is transported to the cytosol and can be used in the production of fatty acids and cholesterol. A carbohydrate-rich diet increases the de novo synthesis of fatty acids and cholesterol by the liver. The synthesis decreases when some of the carbohydrate is replaced by fats. The decrease is even smaller when MCTs, rather than LCTs, are provided in the diet (33–35). The slight cholesterol-lowering effect of MCTs identified by many investigators can be accounted for by a decrease in the intestinal absorption of cholesterol and a slowing of its synthesis from acetyl-CoA in the liver (34, 36). Less cholesterol is synthesized because the acetyl-CoA is used in the de novo synthesis of fatty acids (37); and because the activity of β-hydroxy-β-methylglutaryl-CoA reductase, the key enzyme in cholesterol synthesis, is reduced (34).

After a single oral dose of MCTs a slight hypoglycemia develops (27, 38). It is caused, apparently, by a decrease in the hepatic output of glucose and not by an increase in the peripheral utilization of glucose. Interestingly enough, the concentration of insulin in the blood increases at the same time, because the islets of Langerhans are stimulated either by the ketone bodies or by the MCFAs themselves or by both. But, in general, it appears that MCTs improve carbohydrate tolerance (39, 40).

Extrahepatic metabolism

Given the magnitude of the hepatic uptake of MCFAs, the role of the extrahepatic tissues in the metabolism of MCTs is small, except for the utilization of ketone bodies. The MCFAs, however, play an important role in the human fetus. Pilz (41) reported that 15 to 20% of the fatty acids in cord blood have eight or fewer carbon atoms.

As in the liver, the extrahepatic tissues do not incorporate much MCFAs in the lipids they synthesize (24). In addition, LCFAs diminish the capacity of fat cells to esterify C8:0 (42). As in the liver, it appears that MCFAs do not need carnitine to cross the mitochondrial membrane of extrahepatic tissues. This, however, has been questioned by Groot and Hülsmann (43). MCFAs are oxidized into CO_2 in the extrahepatic tissues more rapidly than are LCFAs (24). Also, as

in the liver, MCFAs inhibit, only slightly, the de novo synthesis of fatty acids in adipose tissue (35).

Clinical use

Fat malabsorption

For 30 yr the special properties of MCTs have been applied in human therapy, particularly in cases where the digestion, absorption, or transport of usual dietary fats are disturbed. In such cases steatorrhea is present and is often followed by a progressive secondary malnutrition caused by the loss of nitrogen, water, and electrolytes in the feces. In general, the steatorrhea subsides when dietary LCTs are replaced by MCTs, and the number and weight of the stools are reduced. The low concentration of lipids in the serum remains unchanged, but the dyspepsia and the nutritional state improves. Patients gain weight and children start to grow again. Thus MCTs have been used successfully in adults, children, and newborns with the following disorders:

1) In disorders of lipid digestion, as with major or total resection of the esophagus or of the stomach; biliary atresia, obstructive jaundice, primary biliary cirrhosis (44), and blind-loop syndrome; and pancreatitis (45), cystic fibrosis (46–48), and pancreatectomy.

2) In disorders of lipid absorption, as when there is massive resection of the small intestine (49, 50), celiac disease, Whipple's disease, Crohn's disease, enteritis, gluten enteropathy, tropical or idiopathic sprues, and malabsorption in neonates (18, 51).

3) In disorders of lipid transport, as in deficiency of chylomicron synthesis (eg, congenital β-lipoprotein deficiency); and in lymphatic disorder due to engorgement (eg, intestinal lymphangiectasia) or leakage [eg, chyluria (52, 53), chylous ascites, and chylothorax (54, 55)]. In the case of an abnormal exchange between the lymphatic system and another system or a cavity, MCTs decreases lipid and protein losses. Since MCTs, unlike LCTs, do not stimulate the flow of lymph, they favor the healing of fistulas.

In cases of maldigestion and/or malabsorption where LCTs are not well tolerated, MCT-containing diets have a great advantage over low-fat diets. The advantage is that MCTs are a fat and thus can be used in cooking. In addition, MCTs are a concentrated source of calories (8.3 kcal/g compared to 3 to 4 kcal/g for carbohydrates and proteins), and a good source of acetyl groups which are useful in lipid synthesis.

The ingestion of labeled fats followed by the detection of the tracer in the expired CO_2 is a method often used to measure the amount of fat absorbed. Since MCTs are oxidized much more rapidly than LCTs, labeled trioctanoylglycerol has been preferred to triolein by Schwabe et al (56) (^{14}C tracer) and by Watkins et al (57) (^{13}C tracer) to detect malabsorption of fats.

Gallbladder disease

The medium-chain monodiglycerides of caprylic and capric acid can be solubilized in aqueous solutions, oils, and other organic compounds. The medium-chain monodiglycerides have been investigated in in vitro (58) and in vivo studies for their use in dissolution of gallstones. A product containing these medium-chain monodiglycerides is under an investigational new drug status in the USA (Capmul 8210, Stokely-Van Camp, Inc, Indianapolis, IN; US patent 4,205,086, May 27, 1980). It has been used successfully in the treatment of cholesterol-related cholelithiasis (59, 60) by perfusing it into the common bile duct. Recently, further advances have been reported in both percutaneous and endoscopic entry techniques confirming the safety, efficacy, and rapid dissolution of gallstones with this product (61, 62).

Application of the energy-providing and ketogenic properties of MCTs

When MCTs are supplied in the diet, they are rapidly oxidized, rendering many ketone bodies and supplying a quick source of energy. The energy is delivered to the whole body, both the liver (during the oxidation of fatty acids), and the extrahepatic tissues (mainly during the utilization of ketone bodies). A modest elevation of the concentration of ketone bodies in the blood is known not to be dangerous: all the extrahepatic tissues can use the ketone bodies supplied by the blood. When the blood level of β-hydroxybutyrate and acetoacetate increases, the utilization of ketone bodies is enhanced (63). These tissues

are enzymatically equipped to produce acetyl-CoA from ketone bodies. The activated acetate is then used according to local needs, either as a source of energy, or as a basic ingredient in the de novo synthesis of lipids.

Sources of energy

The MCTs are, therefore, a food of choice for any organism that has increased energy needs, as after major surgery (64), or during normal or retarded growth (16, 18, 65). It is generally believed that MCTs should be included in the nutritional management of the severe undernourished patient.

Another major consumer of ketone bodies is the fetus. Rubaltelli et al (66) have suggested that the perfusion of LCTs into expectant mothers could help the treatment of the fetus with slow intrauterine growth. From what is known about MCTs, it allows us to think that in this instance, it would be preferable to use MCTs rather than LCTs.

Lipid precursors

The acetyl-CoA produced in the peripheral tissues from MCTs can also enter into anabolic pathways. In the brain, large synthesis of lipids—mainly phospholipids—from ketone bodies have been demonstrated (67). This synthesis appears to be very effective during the period of myelinization of the brain. The use of MCTs as a source of energy and lipid precursors in complicated pregnancies should be further explored.

Anticonvulsive properties

Ketone bodies also have a narcotic and anticonvulsive property that has not yet been explained (68). This property has long been used in the treatment of epilepsy. Although many drugs are now available, a ketogenic diet (69) remains a valuable alternative in anticonvulsive therapy in at least two cases: when there is resistance to the usual drugs (eg, epileptic myoclonia of childhood) and in intolerance to the medication, or both.

In addition to providing an insufficient amount of carbohydrates, a ketogenic diet has the disadvantages of being unpalatable and difficult to prepare and administer. These disadvantages are partially overcome with the MCT-based ketogenic diet introduced by Huttenlocher et al (70) and used with complete success by some authors (71–73). The diet provides 70% of the calories from MCTs, as compared to 87% calories from fat in the LCT-based ketogenic diet. However, some setbacks in the treatment of epilepsy with MCTs have recently been reported (74–77).

Hyperalimentation

MCTs are a preferable food for any organism that has increased energy needs, such as undernourished patients after major surgery (64) or children during normal or retarded growth (16, 18, 65).

The metabolism of MCFAs by the extrahepatic tissues is increased considerably when MCTs are supplied intravenously. MCTs are, consequently, supplied in abundance to the various tissues where they are hydrolyzed. In these tissues, part of the released fatty acids are incorporated into lipids (42), but most of them are oxidized. The resulting acetyl-CoA generates energy in situ and contributes to lipid synthesis. The caloric demands of the stressed patient are difficult to meet without incorporating fat into the parenteral regimen. Lipid emulsions containing LCFAs, which for the most part are stored in the hepatic and adipose tissues, are not capable of supplying quick energy in large quantities. Therefore, replacement of LCTs with MCTs could be valuable. Sailer and Berg (64) showed that emulsions of LCTs containing 25 or 50% MCTs were very useful in patients requiring intensive nutritional therapy. The MCTs were rapidly removed from the circulation, the increase in ketonemia was within acceptable levels, and the tolerance to these fats was excellent, even in protracted therapy. In chronically ill patients in critical condition, MCTs not only cover the energy needs, but also contribute a sparing action for the lowered muscular carnitine levels (78) and correct the depression in ketonemia (79) related to septicemia or trauma.

In recent years with the introduction of structured lipids based on the MCTs as the main backbone of the lipid, we are seeing modifications of MCTs which improve their utility and nutritional suitability in hyperalimentation. Although physical mixtures of MCTs and LCTs have been tried in parenteral nutrition (64, 80, 81), such mixes demonstrate the dual pattern of clearance and

energy utilization of MCTs and LCTs. With the advent of structured lipids of MCTs and LCTs at random distribution in the same triglyceride molecule, there is now the potential for tailor-making of lipids to meet the physical and nutritional needs of patients receiving parenteral or enteral nutrition. Babayan (82) has projected the types of structured lipids that are available for clinical investigations. Such structured lipids promise real progress in the hyperalimentation field where lipids and high-density calorie requirements are sought by the physician.

Hyperlipidemias

Because MCFAs are incorporated into lipids only in small amounts, many studies have been performed to find out whether MCTs can be useful in the treatment of hyperlipidemias.

Although some authors (32, 34, 36, 83, 84) have reported their observations on the decrease in blood and liver cholesterol levels with an MCT diet, we do not have a clear picture of the role MCT can play in the treatment of hypercholesterolemia. This area deserves further study.

In view of present knowledge of the causes of hyperlipidemias, it is clear that MCTs have no role in their treatment, except in type I (lipoprotein lipase deficiency, mast-cell deficiency) and in type V (diminished activity of lipoprotein lipase) hyperlipoproteinemias. Since in these cases the clearing enzyme, or its coenzyme are absent or insufficient, the replacement of dietary LCTs with MCTs (85) has been very useful in the treatment of these disorders. In studies done in rats, MCTs, unlike LCTs, slowed down the appearance of alcoholic steatosis (86) and speeded up the regression of established atherosclerotic lesions, when alcohol was withdrawn from the diet (87).

Malmros et al (88) found that an MCT-based diet fed to rabbits induced atheromatous changes in the aorta and coronary arteries. The diet, however, was probably deficient in polyunsaturated fatty acids. In contrast, the following observations have been made in the rat. *1*) The aorta almost completely oxidizes MCFAs into Co_2 (89). *2*) MCTs limit the deposition of cholesterol in all tissues (84, 90). *3*) MCFAs are not thrombogenic, while saturated LCFAs are (91) thrombogenic. *4*) The life span is longer when the diet is richer in MCTs than in LCTs (92).

Deficiency of the carnitine system

In skeletal muscle, the transport of LCFAs from the sarcoplasm into the mitochondria is dependent on the carnitine system. Therefore, a deficiency of carnitine or carnitine palmityl transferase (I or II, or both) results in a diminished capacity to oxidize LCFAs (93). The lowering of this energy catabolism, which is essential for the working muscle, is manifested by various symptoms: muscular weakness, pain after exertion, myoglobinuria, lipid-filled vacuoles within muscle fibers, and episodes of metabolic encephalopathy. As the fatty acids continue to reach the muscle, they are incorporated into triacylglycerols, which accumulate. In the myopathic form of carnitine deficiency, the pathology is limited to the skeletal muscles, but in the systemic form the heart, liver, and kidneys are affected.

In view of the particular intramitochondrial transfer of the MCFAs, patients suffering from a deficiency of muscular carnitine have been treated rather successfully with an MCT-based diet (93–97). In some instances, carnitine was added. However, the disorders observed in patients with carnitine palmityl transferase deficiency did not always regress when treated with a diet providing MCTs (98, 99). The more or less marked success of treatment with MCTs is probably due to the fact that only a small amount of MCFAs reach the muscle. Undoubtedly, more studies in this area are necessary. Studies on the effect of intravenous MCT infusion would be of special interest in this regard.

Obesity

Animal studies on the effect of the incorporation MCFAs into the adipose tissue have shown that MCTs can produce a slight reduction (not always statistically significant) in body weight, and in the weight of the adipose tissues (33, 35, 100–105, Geliebter A, Torbay N, Bracco EF, Van Itallie TB, Hashim SA, unpublished data). The food efficiency ratio is diminished in rats fed MCTs (104, 107): the animals need to consume 20.3 kcal/g of weight gain when fed MCTs as compared to 16.6 kcal/g of weight gain with LCTs. The reason for the lowered food efficiency ratio seems to be an enhanced

thermogenesis induced by MCTs (105). Kaunitz et al (108) found that the weight of normal and obese subjects diminished when LCTs were replaced with MCTs in their diet.

The value of MCTs in obesity is not as yet well understood. The results of Rath et al (83) failed to provide any evidence in favor of MCTs. In their study, obese women given a 550 kcal diet containing 30 g of MCTs lost as much weight as when MCTs were replaced by sugars. Kaunitz et al (109) found that obese subjects consuming a 1200 kcal diet lost the same amount of weight whether the dietary fat was olive oil or MCTs. In the genetically obese Zucker rat (110) and the BHE rat (111), an MCT diet did not reduce body weight.

Nevertheless, several reports indicate that MCTs may be a useful tool in the control of obesity. Lavau and Hashim (35), Schemmel (104), Travis et al (105), Turkenkopf et al (112), Geliebter et al (106), Baba et al (113), Bray et al (114), and Bach et al (115) indicate a reduction of carcass mass with the use of MCTs. In view of these conflicting results in the literature, additional studies are needed to understand the role of MCTs in the treatment of obesity. One explanation for these results could be that the nonincorporation of MCFAs into the adipose tissue is more or less compensated for by the weak inhibition of de novo synthesis of fatty acids by the liver and adipose tissue (35).

The monoesters and diesters of polyglycerols containing MCFAs can be considered as replacements for natural fats. These polyglycerol esters appear to have the ability to impart a feeling of satiety while eliminating and/or reducing the lipid level in a food product, while still maintaining the desired appearance and physical form. Their energy value is only 6 to 8.5 kcal/g. The use of these esters in foods will be a convenient way to reduce calories, particularly fat calories (116).

Contraindications

Ketosis and acidosis

MCTs are ketogenic in the normal subject and even more in the patient with hyperosmolar diabetic syndrome (117). Hence, MCTs should not be given to patients with diabetes. They should also not be given to patients with ketosis or acidosis. In these conditions, the capacity of the extrahepatic tissues to use ketone bodies is saturated. Therefore, the additional supply of such substrates is not only wasted as an energy source, but it also aggravates the metabolic acidosis and accelerates the breakdown of the homeostatic mechanisms. The solution to this problem may be using MCTs with odd carbon chain fatty acids instead of the even carbon chain fatty acids. Indeed Guy and Tuley (118) showed that tripelargonin is less ketogenic than usual MCTs in rats.

Cirrhosis

Since MCFAs are metabolized mostly in the liver, the intestinal perfusion of octanoate in healthy subjects results in the appearance of only small amounts of this fatty acid in the circulating blood (119). However, when the functional cell mass of the liver is reduced, as in cirrhosis, the C8:0 concentration in the blood increases due to the reduced hepatic clearance. In the case of a portacaval shunt, for example, C8:0 reaches very high amounts (119). It is generally believed that fatty acids are somewhat toxic when given in large amounts. Intravenous infusion of C8:0, for example, results in a syndrome resembling hepatic encephalopathy: hyperventilation, hyperammoniemia, hyperlactacidemia, and disturbed electroencephalogram (120, 121). In healthy subjects, the binding of fatty acids to albumin in the serum relieves this toxicity. But, in cirrhosis, the albuminemia drops. In addition, the affinity of MCFAs for albumin is weak, because LCFAs and MCFAs compete for the albumin binding sites (122). Under these circumstances, free fatty acids, not bound to protein, diffuse passively across the capillary membranes. Thus, free octanoic acid has been found, not only in the blood, but also in the ascitic fluid, and the cerebrospinal fluid of persons with cirrhosis who were given this fatty acid by intestinal perfusion (123). It appears that, in cirrhosis, there is the danger that the energy metabolism of the brain may be altered.

Availability and suggestions for use

Initially, MCTs were available only in the form of oil or margarine. MCTs are now available in liquid or solid preparations and in simple or complex combinations with pro-

teins, sugars, vitamins, essential fatty acids, and minerals. These various forms make it possible to provide the infant or the adult with the amounts of MCTs needed for parenteral, oral, or tube feeding (124).

It is indispensable to determine for each patient the threshold dose that must not be exceeded if problems are to be prevented from arising, eg, osmotic diarrhea in ileitis and in extensive resection of the small intestine, or in dumping syndrome in patients with gastrectomy.

In enteral feeding, MCTs should first be introduced in small amounts and gradually increased to the prescribed dose. In general, MCTs are well tolerated when the daily dose is divided proportionally into meals of a well-balanced diet. MCTs diets seem to be better tolerated by children than by adults (90). A nutritionally balanced diet is the best way of avoiding ketosis. A daily supply of 50 or even 100 g is easily tolerated. Obviously, when MCTs are given for their ketogenic properties the procedure will be different (68, 75).

MCTs are not a panacea. Only rarely do MCTs alone provide the best therapeutic solution. Very often, it is advisable to combine MCTs with the standard therapy of the particular illness: a reduction in the supply of LCTs, or the provision of bile salts (in biliary deficiency), enzyme therapy (in pancreatic deficiency), a gluten-free diet (in celiac disease), antibiotics (in tropical sprue), or carnitine (in carnitine deficiency).

It must be remembered that when the digestion or absorption of LCTs is perturbed, a smaller amount of MCTs is absorbed than in the healthy organism; but in any case more MCTs are absorbed than LCTs. As discussed previously, the ingestion of large amounts of MCTs decreases the absorption of LCTs, and increases the losses of LCFAs in the feces. Nevertheless, extrapolating the results obtained in rats to patients with reduced lipid absorption, Clark and Holt (12) suggested that the amount of LCTs normally tolerated could be doubled, by means of an MCT supplement, without inducing steatorrhea.

When MCTs are infused parenterally, the dose should be carefully calculated and the patient closely monitored. If the dose is in excess, there is danger of acidosis due to hyperketonemia and hyperlacticacidemia (125).

In total parenteral nutrition, the essential fatty acids should be included in the regimen. While Kaunitz et al (126) showed in the rat that MCTs lowered the need for linoleic acid more than LCTs, Hirono et al (127) reported that the need for this fatty acid was increased in newborn babies given an MCT-based milk. Williams and Oski (128) found no change in the vitamin E status of newborn babies fed MCT-based milk. It is, therefore, important that when MCTs are given intravenously or enterally as the sole source of fat, that the needs for essential fatty acids are met. There are now available tailor-made MCTs with varying amounts of linoleic acid (Captex 810, Stokely-Van Camp, Inc) These products are facilitating the design of regimens that meet the essential fatty acid requirements of patients.

When MCTs are used for cooking or frying, they should not be heated to temperatures above 150 to 160°C. Above this temperature, it will result in oxidation and thermal breakdown which will affect the palatability and acceptability of the product.

Conclusions

The particular physicochemical properties of MCFAs make MCTs a valuable tool in the dietetic management of a number of disorders of lipid metabolism. Most fat maldigestion and malabsorption conditions, and some disorders of the lymphatic fat transport and of the fat removal from the blood, can be completely or partially corrected by replacing dietary LCTs with MCTs. The crucial needs for energy or for acetyl-CoA as precursors of lipids, can be met by a supply of MCTs, whether the need is transient or long lasting.

Although MCTs are fats, they tend sometimes, to behave like carbohydrates. Although MCTs are oxidized rapidly and have low tendency to be stored in the adipose tissue, MCTs are not hyperlipidemic, but they are ketogenic. Although MCTs are not hyperglycemic, they slightly stimulate insulin production, but do not lower lipogenesis significantly. MCTs are not drugs—they have no pharmacological effect.

In summary, the beneficial effects of MCTs are: *1*) MCTs are digested, absorbed, and transported easily and rapidly in disorders where the digestion, absorption, or transport

of LCTs are not optimal. *2*) MCTs are oxidized rapidly in the organism and they have a very low tendency to deposit as body fat. *3*) MCTs are a source of abundant and rapidly available energy. *4*) MCTs are ketogenic. *5*) MCTs are donors of hydrogen ions and precursors of acetyl-CoA.

MCTs do not behave as conventional fats. Thus, MCTs must be treated separately and differently from our understanding of fats and oils. The unique physical, chemical, and structural characteristics of MCTs and their modifications (structured lipids) makes such special lipids tools for solving certain medical problems.

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