Chapter 2

Digestion and Absorption of Glycerides

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Introduction

The major components of most food fats are triacylglycerols (TAG). TAG molecules can differ from each other in the fatty acids they contain and in the combination and/or stereochemical implantation of different fatty acids on the glycerol backbone. Other components with distinct nutritional effects that can be present in food fats are partial glycerides, phospholipids, sterols, fat-soluble vitamins and provitamins, antioxidants, and other fat-soluble components, some of which can affect gene expression.

By chemical and enzymatic processes, the structure of TAG can be modified and minor natural fat components such as monoacylglycerols (MAG), diacylglycerols (DAG), and phytosterol esters can be produced in large quantities. These have been shown to have special nutritional properties. This is also the case for TAG with changed stereospecific position or changed combination of fatty acids such as interesterified fats (1), structured lipids (2), or salatrims (3). DAG and MAG also have nutritional effects different from TAG with the same fatty acid composition.

The structural effects of food fats on several of their physiologic, nutritional, and pathophysiologic properties can be understood on the basis of a combination of their effect of gastric emptying, specificity of enzymes that are involved in lipid digestion, rate of uptake of their digestion products, and further metabolism of the latter. In this chapter, integrated aspects of digestion, absorption, and interactions of the absorbed products in the intestinal cell will be discussed.

Metabolism of Dietary Fat

Gastric Phase of Fat Digestion and Absorption

Except for experimental settings, fats are always consumed as part of a meal, which also contains nonfat constituents such as carbohydrates, proteins, or fiber. These components may affect phenomena related to fat digestion and absorption. Thus, results of experiments using fat loading or infusion of fat emulsions in the stomach or in the duodenum may not be fully applicable to real-life situations.

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Physicochemical Reactions in the Stomach. An average Western diet contains ~100–150 g food fat, with ~97% of this as TAG. The remainder is made up of phospholipids (4–8 g/d, mainly phosphatidylcholine), cholesterol, other sterols, and minor lipid components. When they are the only lipids present in an aqueous environment, TAG form unstable emulsion droplets, whereas phosphatidylcholines form relatively stable lamellar structures. When TAG and phospholipids are present together in proportions as found in the diet, the latter act as an emulsifier by coating the TAG droplets, thus forming more stable emulsions. Proteins and their peptic digestion products stabilize TAG emulsions in the stomach and in the intestinal lumen (4). Gastric lipolysis helps to increase emulsification in the stomach (5). Stabilized emulsion droplets are substrates for gastric lipase. A lower initial droplet size facilitates gastric and intraduodenal digestion (6). When viscous soluble fiber is present in the diet, the size of the emulsion particles is increased, and their subsequent rate of lipolysis is reduced (7).

DAG and MAG with thermodynamic equilibrium composition (*eq*-DAG and *eq*-MAG) are easily prepared industrially in large quantities. Such DAG are on the market as edible oils in Japan and in the United States. *eq*-DAG and *eq*-MAG are also used in smaller quantities as emulsifiers in some foods. *eq*-MAG, alone or in combination with medium-chain triglycerides (MCT), were used successfully to correct digestive malabsorptions and consequences thereof (8). Long-term effects of *eq*-MAG (9,10) and *eq*-DAG feeding (described in several chapters of this book) and postprandial effects of loading with these special fats were documented (see below). When DAG are fed as part of a meal, they probably also form small emulsion droplets in the stomach. MAG form in an excess of water lamellar liquid crystalline phases at body temperature (11). Their swelling can be affected by the presence of other substances (12). When MAG are present with TAG in excess, they will likely form co-emulsions.

Gastric Digestion. In humans, the hydrolysis of TAG starts with the action of gastric lipase. Gastric lipase preferentially splits primary ester bonds, although there may be some hydrolysis from fatty acids esterified at the *sn*-2 position (13). It does not act on phospholipids or on cholesteryl esters nor is its activity inhibited by phospholipids (14). With TAG as substrate, gastric lipase catalyzes the hydrolysis of the fatty acid at the *sn*-3 position preferentially to that at the *sn*-1 position (15) and prefers TAG with short and medium chain lengths. Thus, TAG with such fatty acids in the *sn*-3 position as are present in bovine milk and its products are preferential substrates. As a result of product inhibition by free fatty acids (FFA), the main digestion products of gastric lipase are FFA and *sn*-1,2 DAG when TAG are the substrate (16). It was demonstrated that *sn*-1,3 DAG also comprise substrates for gastric lipase but that with these substrates, the enantioselectivity for the *sn*-3 position no longer exists (17). In a monolayer system, *sn*-1,3- and *sn*-2,3 dicaprin are equally good substrates for human gastric lipase, but there is discrimination against 1,2 dicaprin (18). It is likely that in co-emulsions of DAG with TAG, the former would be enriched in the outer layers of the fat droplets. Whether this would result in preferential hydrolysis is not known. It is not

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clear whether *sn*-1(3) MAG, which would be formed by gastric lipolysis of *sn*-1,3 DAG or fed as such, would be substrates for gastric lipase.

It was demonstrated that medium-chain fatty acids, which are set free in the stomach, can be absorbed directly into the portal blood and thus affect hepatic metabolism (19). The specific activity of gastric lipase *in vivo* is comparable to that of pancreatic lipase for liquid fats and higher for solid fats (20). Of course, pancreatic lipase output is much higher than gastric lipase output. High-fat diets increase gastric lipase output in humans (21). About 10% of the dietary fatty acids are liberated by gastric lipase from a test meal that contains TAG with long-chain fatty acids, but considerably higher amounts from a test meal that contains TAG with short- or medium-chain fatty acids (22).

Even for long-chain fatty acid–containing TAG, this corresponds to the breakdown of about one third of the TAG into DAG and FFA in the stomach. Furthermore, there is evidence that gastric lipase is also active in the upper small intestine. The importance of gastric digestion is that its hydrolysis products affect the excretion of some hormones involved in fat digestion, thus helping to stabilize the surface of the TAG emulsion. This promotes the binding of pancreatic colipase later in the small intestine, thus making it a better substrate for pancreatic lipase (23). There is a compensatory increase in gastric lipase when pancreatic lipase is low. Nonetheless, under these conditions, the capacity for fat absorption remains limited when usual food fats are fed. It can be expected that under these conditions, the lipids of choice to enable feeding more fat and provide for energy and essential fatty acids would be semisynthetic triglycerides with a short-chain fatty acid at the *sn*-3 position and long-chain fatty acids that include essential fatty acids at the other positions.

Gastric Emptying. If gastric digestion is allowed to proceed long enough, the fat mixture that will be emptied into the upper small intestine will have an equilibrium composition governed by product inhibition (16). If not, its composition will depend on the rate of gastric digestion and on the time the dietary fat was retained in the stomach. The physicochemical and chemical forms in which dietary fats are consumed affect the rate of gastric emptying. Fats that are ingested as emulsions are partitioned into an aqueous phase and an oil phase, whereas fats consumed as nonemulsions form an oil phase. Fats in the aqueous phase are readily emptied from the stomach, whereas fats in an oil phase are emptied much more slowly (24). The chemical composition of the oil phase also influences the rate of emptying. The delaying effect depends on the saturation (25) and the chain length (26) of the fatty acids. No data are available concerning the effect of the chemical structure of the fat if any. In healthy individuals, the rate of gastric emptying can be rate limiting for fat absorption (27). Fat digestion has an important role in the regulation of postprandial gastric acid secretion and fat emptying in humans. Lipase inhibition accelerates gastric emptying of both the solid and fat phases of a mixed meal (28). No experimental data are available on the rate of gastric emptying of DAG and MAG relative to that of TAG. This may well depend on the physicochemical form in which they are present in the stomach (29).

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Small Intestinal Phase

Lipids in the Lumen of the Small Intestine. The lipids that are emptied from the stomach into the small intestine are diluted by lipids of endogenous origin (~10–25g/d when fasting). Endogenous lipids originate primarily from sloughed intestinal cells and biliary secretions. The amount of phospholipids of biliary origin (7–22 g/d, mainly phosphatidylcholine) is considerably greater than that of dietary origin (3–8 g/d) (30). The same is also often true for cholesterol (~1 g/d of endogenous origin). In bile, bile salt-phospholipid mixed micelles exist in a cylindrical arrangement (31). In the intestinal lumen, bile salts and phospholipid molecules are likely to partly adsorb to the lipid emulsion droplets.

Overview of Reactions in the Small Intestine. The main reactions occurring simultaneously or quasi-simultaneously in the small intestine are digestion of the glycerides in the emulsion phase, isomerization of partial glycerides in the emulsion phase, transfer of the digestion products from the emulsion phase into micellar phases, digestion and isomerization in the micellar phase, and uptake of digestion products mainly from micellar phases. Thus, the relative amounts of the different digestion products that will be taken up by the intestinal cells will depend on the relative rates of these different reactions.

Lipolysis. The major enzymes involved in fat digestion in the intestinal lumen are pancreatic lipase, pancreatic phospholipase A_2, and pancreatic cholesterol esterase, the last-mentioned also named bile-salt–dependent lipase. These enzymes work in concert with each other to yield the final reaction products.

Human pancreatic lipase catalyzes the equilibrium reaction between ester formation and hydrolysis. It is specific for primary alcohols and esters of such alcohols. Thus, under certain conditions, pancreatic and other lipases can be used for the synthesis of TAG with certain stereospecific properties (32). Lipases act on the lipid/water interface. In the beginning of and during fat digestion, the lipid/water interface is rich in water and the digestion products are continuously removed from the interface favoring lipolysis. Pancreatic lipase splits off fatty acids from the *sn*-1 and *sn*-3 position of TAG. It is more active against *sn*-1,2- and *sn*-2,3 DAG thus formed than against TAG (33).Thus, it can break down the TAG into *sn*-1,2- and *sn*-2,3 DAG, which can be further hydrolyzed into *sn*-2 MAG. These are no longer substrates for pancreatic lipase. Pancreatic lipase is less active against polyunsaturated fatty acids with a double bond close to the ester bond, in particular when these are located in the *sn*-3 position (34) and clearly prefers the *sn*-1 position of both TAG and DAG (17). Thus, if there would be neither isomerization nor absorption of DAG and MAG, the ultimate digestion products of TAG would be a 2:1 mixture of FFA and *sn*-2 MAG. However, both reactions do occur (see below).

Phospholipase A_2 hydrolyzes the fatty acid esterified at the *sn*-2 position in phosphatidylcholine to yield lysophosphatidylcholine and FFA (35). This reaction is of importance for the digestion and uptake of neutral glycerides because the presence of

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phospholipids in the intestinal lumen retards TAG digestion (36), affects the partitioning of lipid digestion products between the oil and micellar phase (37), and slows down the uptake of lipid digestion products from the micellar phase (38). If sphingolipids were present in the diet, they are broken down by sphingomyelinase and the resulting ceramide by ceramidase. Carboxyl ester lipase hydrolyzes sterol esters. It prefers substrates present in the micellar state but has low activity against MAG (39). Cholesterol is absorbed as free sterol, and the effects of phytostanol esters and phytosterol esters are mediated by the free phytostanol/sterol.

Isomerization Reactions. "Linear" partial glycerides are thermodynamically favored over "branched" partial glycerides. MAG with equilibrium isomeric composition consist of ~45% *sn*-1-, 45% *sn*-3- and 10% *sn*-2 isomers (9). For DAG, the isomer ratio is ~ 70:30 (40) for *sn*-1,3- and *sn*-1,2- plus *sn*-2,3 DAG respectively. Isomerization of partial glycerides yields products with primary ester bonds, which are substrates for pancreatic lipase, thus resulting in more complete digestion with the liberation of glycerol. Because MAG are readily absorbed, the rate of isomerization relative to that of uptake is important for further digestion. The isomerization rate increases with unsaturation and decreases with chain length (41). Nonetheless, spontaneous isomerization of long-chain fatty acids containing *sn*-2 MAG in model systems is low compared with their intestinal uptake (42); ~15–20% of *sn*-2 MAG would isomerize in the intestinal lumen (43).

Uptake of Glycerides by the Intestinal Cells. For a lipid to be a candidate for absorption, it must be able to reach the absorptive surface of the small intestine. This is the surface of the microvilli. Geometrically, they are so close to each other that emulsion droplets are too large to come between them. Moreover, an "unstirred" water layer lines the microvilli. Passage through this layer is rate limiting for fat absorption. MAG and FFA leave the emulsion/water interface where they were formed by the action of pancreatic lipase and form mixed micelles with conjugated bile acids. Only in this form can they easily access the absorptive surface of the small intestine and be absorbed. To my knowledge, no data are available on the effect of isomer structure or fatty acid composition of the MAG on the rate at which they are transferred from the emulsion phase to the micellar phase. Partitioning of fatty acids between the emulsion interface and the micellar phase depends on pH. When pH is low, such as in the absence of pancreatic juice, protonated fatty acids remain at the interface of the emulsion and inhibit further digestion, even when pancreatic lipase is administered. The interior of the MAG/FFA/conjugated bile salt mixed micelle is a lipophilic environment in which lipophilic substances such as cholesterol, carotenes, fat-soluble vitamins, and so on can dissolve. It is in this way that they can reach the absorptive surface and are candidates for uptake (44). Lysophosphatidylcholines formed by the digestion of phosphatidylcholines favor micellar solubilization and uptake of fat digestion products (45) and other dietary lipophilic substances (46). Phytosterols can compete with cholesterol for incorporation into the micelles and thus interfere with cholesterol absorption.

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Lysophosphatidylcholine itself is taken up by the intestinal cell, affects intestinal metabolism (47), and can be converted into phosphatidylcholine again. There is evidence that phosphatidylcholine can be taken up intact and excreted as part of intestinal lipoproteins in the lymph (48).

When *eq*-DAG are fed in a diet, TAG are also inevitably present. It is expected on theoretical grounds that they will form emulsion droplets in the stomach together with the TAG. The *rac*-1,2 isomers are normal intermediates of TAG digestion. The *sn*-1,3 isomers, which are the major isomers in *eq*-DAG, would be formed from TAG only in very small quantities by isomerization of their intermediary *sn*-1,2(2,3) DAG digestion products. If pancreatic lipase preferentially attacks the *sn*-1 position of 1,3 DAG as it does in TAG, the major first digestion product would be *sn*-3 MAG, but *sn*-1 MAG would be formed as well. The type of isomer formed would be of no consequence if both MAG isomers, which are substrates for pancreatic lipase, would be broken down completely to glycerol and fatty acids before absorption. However, if there would be substantial absorption of the intact MAG, their isomeric composition could be of importance because it has been shown that they are handled differently in the intestinal cells (see below).

The composition of the mixed micelles that exist in the intestinal lumen and several of their physicochemical properties were described (49). It cannot be excluded that after *eq*-DAG or *eq*-MAG feeding, the geometrical structure of the mixed micelles could be different than after TAG feeding and could affect the extent of micellar solubilization and uptake of other lipophilic substances; however, experimental data are lacking.

Reaching the absorptive surface of the small intestinal cells is not enough for uptake. Bile salts, for instance, are not absorbed at this site, and absorption of phytosterols is very limited. After TAG feeding, long-chain fatty acids that were present in the *sn*-1,3 position are taken up mainly as FFA, whereas those at the *sn*-2 position are taken up mainly as *sn*-2 MAG. In contrast to long-chain fatty acids, medium-chain fatty acids are mainly but not exclusively taken up as FFA whatever their position in the medium-chain or mixed-chain TAG ("structured lipids") that were present in the diet.

There is some evidence to suggest that small amounts of TAG and DAG can be taken up without prior digestion. After consumption of MCT, small amounts of these triglycerides were found in ascites fluid from a patient with an obstruction of the thoracic duct (50), suggesting that small amounts of TAG (at least MCT) can be taken up without prior intestinal digestion. Postprandial and long-term effects after oral administration of MAG suggest that part of them may be taken up intact (see below). Some of the postprandial effects after feeding of DAG suggest that part of them may be taken up as MAG.

Intestinal Metabolism of Fat Digestion Products

Intestinal Handling of FFA. In the cells of the small intestine, several enzymes can act on free but not on esterified fatty acids. In contrast to MAG, FFA are diluted with

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fatty acids originating from the plasma free fatty acid pool (51). After activation, they can be oxidized, elongated, chain desaturated, and converted into complex lipids (51,52). The relative rates of the different metabolic routes depend on the nature of the fatty acids and on the presence of other components in the intestinal cells (53). Conversion of saturated fatty acids into monounsaturates when they are absorbed in free form, i.e., when they were present in the outer position of the dietary TAG, could contribute to their lower hypercholesterolemic effect than when originally present at the inner position. FFA also affect intestinal gene expression (54) and the production of apolipoproteins; these effects are fatty acid dependent (55). When *sn*-2 MAG are simultaneously present in the intestinal cells, as after TAG feeding, FFA are converted mainly by a multienzyme complex in TAG that are excreted as chylomicrons. The excess of FFA reacts with *sn*-3 glycerophosphate to form lysophosphatidic acids, which are further converted into phosphatidic acids. Dephosphorylation results in *sn*-1,2 DAG, which are precursors of both TAG and phospholipids. This results in the formation of intestinal lipoproteins of smaller size (56).

Intestinal Handling of α-Monoglycerides. What will happen after influx of 1(3) *sn*-MAG in the intestinal cell is less clear. A series of competing reactions must be considered such as complete digestion, acylation, transacylation, phosphorylation, or intact excretion out of the intestinal cells. Lipases that hydrolyze MAG are present in the intestinal cells but their action seems to be reduced by other intestinal cell constituents (57). Some of them show obvious fatty acid specificity (58). Both *sn*-1- and *sn*-3 MAG can be acylated to form *sn*-1,3 DAG. This transformation is fatty acid and species dependent (59). Nonetheless, *sn*-1,3 DAG are poor substrates for intestinal TAG synthesis (59,60). *Sn*-1- but not *sn*-3 MAG can be phosphorylated into lysophosphatidic acid (61) and possibly be metabolized further as described above. If MAG would escape intestinal metabolization and could leave the cell intact, they could be transported to the liver by portal blood bound to albumin (62). Portal absorption of MAG with medium-chain fatty acids was documented (63). It was demonstrated that cultured liver cells convert *sn*-1 glycerol monoethers (*sn*-1 MAG analogs) into phospholipids and triglycerides (64).

There is some indirect evidence that after MAG feeding, intact *sn*-1 MAG or their phosphorylated derivatives reach the liver with retention of the *sn*-1 ester bond. After long-term feeding of *eq*-monolinoleate, carbon number analysis (separation and quantization according to the sum of the chain lengths of the three fatty acids present) of fasting serum TAG revealed an increased ratio of TAG species with carbon number 54 relative to 52. The former TAG combine fatty acids with chain length 18/18/18, whereas the latter have 16/18/18 as their chain length combination (10). This finding was interpreted as follows. In the liver, TAG synthesis starts with *sn*-3 glycerophosphate as the initial fatty acid acceptor. *Sn*-3 glycerophosphate acyltransferase shows fatty acid chain length selectivity, incorporating ~60% fatty acids with 16 carbon atoms and 40% fatty acids with 18 carbon atoms at the *sn*-1 position. The other enzymes involved in hepatic synthesis of TAG that will be secreted in plasma (65)

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incorporate mainly unsaturated fatty acids with 18 carbon atoms (~ 80%). As a result, the main chain length combination of fatty acids in TAG in fasting plasma will be 16/18/18 as was found experimentally.

By feeding *sn*-1 MAG, the fatty acid selectivity of *sn*-3 glycerophosphate acyltransferase could be bypassed on the condition that these were phosphorylated and thus converted into lysophosphatidic acids. Phosphorylation of *sn*-1 monoglycerides by intestinal and liver cell homogenates was demonstrated (61,64). If these *sn*-1 MAG–derived lysophospholipids would be further metabolized in the same way as the *sn*-3 glycerophosphate–derived lysophospholipids, TAG would be formed with the main fatty acid combination X/18/18, with X as the chain length of the fatty acid in the *sn*-1 position of the MAG. If this reasoning is correct, there should be a preferential increase in the fraction of TAG with the chain length combination 18/18/18 if *eq*-monolinoleate was fed. This was indeed the case. The carbon number composition of fasting serum triglycerides after long-term natural fat or eq-MAG feeding is given in Figure 2.1.

If the concept that the fatty acid specificity of *sn*-3 acyltransferase can be circumvented by feeding *sn*-1 MAG that contain at the *sn*-1 position a fatty acid that normally is not incorporated into lysophosphatidic acid is correct, TAG with unusual struc-

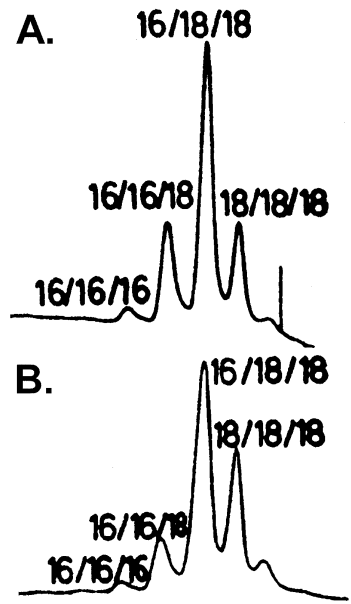

FIG. 2.1. Carbon number composition of serum triglycerides after long-term feeding of a diet with usual food fats (mainly triglycerides) (panel A) or a diet in which the visible food fat was replaced by eq-monolinoleate (panel B). Conditions: 3% JXR, 80 cm; He 40 mL/min; Ts = 150°C; r = 4°/min; TE = Tdetector = 330°C; on column injection.

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tures may be formed. Such "plasma TAG with unusual structure," which may also occur after DAG feeding in case these are partly taken up as MAG, may be turned over at different rates and consequently affect their fasting concentration.

Postprandial Effects

After TAG feeding, long-chain fatty acids leave the intestinal cell mainly as TAG incorporated into intestinal lipoproteins with the size of chylomicrons. These are transported *via* the lymphatic route. When they enter the blood stream, there is an increase in chylomicronemia and triglyceridemia, and the fatty acid composition of plasma TAG changes toward that of the fat fed (66). Chylomicron-TAG are hydrolyzed by lipoprotein lipase, resulting in the formation of remnants and the liberation of FFA. As a consequence, the composition of the nonesterified fatty acids in plasma also changes toward that of the fat fed. Chylomicron remnants are taken up by the liver. Medium-chain fatty acids provided in the diet as MCT or as structured lipids are transported mainly as FFA by the portal vein (67).

After isomeric *eq*-MAG loading, the well-known postprandial chylomicronemia, triglyceridemia, and shift of the fatty acid composition of serum triglycerides and nonesterified fatty acids toward that of the fat fed are much less pronounced than after natural fat feeding (68). However, when MAG are fed together with FFA, effects similar to these of TAG feeding occur. This finding agrees with the finding that the availability of long-chain FFA in the intestine is critical for chylomicron synthesis (69). MAG feeding in normal volunteers does not result in increased fecal fat, indicating that these fats are absorbed as completely as TAG. In patients with pancreatogenic digestive malabsorption, they are better absorbed (8). MAG loading does not result in the appearance of MAG or DAG in blood in the postprandial state.

The reduced hypertriglyceridemia and chylomicronemia after MAG loading (56,68) in combination with the absence of increased stool fats or the appearance of MAG or DAG in blood in the postprandial state suggest that at least part of the fatty acids fed as MAG is not transported by the lymphatic system but by the portal vein. Influx of these components into the liver could initiate a cascade of reactions, which may explain the appearance of "unusual" triglycerides in the circulation (see above), lower adiposity, and lower insulinemia and leptinemia (40). The concept of portal transport of MAG based on findings in humans contrasts with findings in rats. When docosahexaenoic acid was administered intragastrically in emulsion form in lymph-cannulated rats as MAG, lymphatic output (mainly as TAG) was higher than when administered as TAG (70). It is not known whether this is due to the differences in experimental set-up or to species differences.

Loading MAG together with FFA results in TAG effects in the postprandial state (Table 2.1). Loading with FFA results in effects that are different from these obtained after loading with MAG or TAG (Table 2.1). *eq*-DAG feeding has postprandial effects distinct from feeding TAG with the same fatty acid composition. For instance, in rat liver, decreased activities of enzymes involved in fatty acid synthesis and increased activity in those involved in fatty acid oxidation were found after DAG

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TABLE 2.1
Postprandial Lipemic and Lipoproteinemic Effects of Feeding TAG[a], *eq*-DAG[b], *eq*-MAG[a], and a 2:1 Mixture of FFA + *eq*-MAG[a]

Effects	TAG[a]	DAG[b]	Fat fed MAG[a]	FFA	MAG[a] + FFA
Chylomicronemia	+++	++	±	+	++
VLDL increase	+	ND	–	+++	+
Triglyceridemia	+++	++	±	+++	+++
On fatty acids[c]	+++	ND	+	+++	+++

[a]With the fatty acid composition of sunflower seed oil (56,68).
[b]With the fatty acid composition of olive oil (70).
[c]Change of the fatty acid composition of fasting plasma triglycerides toward that of the fat fed
ND, no data available.

compared with TAG feeding. It is conceivable that *sn*-1,3 DAG will be partially digested and taken up as 1(3)-MAG and FFA. Indeed some of their postprandial effects mimic those of isomeric *eq*-MAG feeding, e.g., a lower increase in chylomicron TAG (71). The postprandial lipemic/lipoproteinemic effects of feeding TAG, DAG and MAG(**AQ3**) are summarized in Table 2.1.

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