Synthetic and modified glycerides: effects on plasma lipids

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It has been suggested that the molecular species or structure of the triglyceride, i.e. not only what fatty acids are present but also their relative order in the sn1, 2, or 3 position on the triglyceride, can influence the metabolism of the triglyceride and its fatty acids, including lipoprotein metabolism. One rationale for this possibility assumes that the fatty acid in the sn2 position can be absorbed intact, i.e. as the sn2 monoglyceride, whereas the sn1,3 fatty acids are absorbed as free fatty acids that metabolize independently. Some sn2 monoglyceride might ultimately serve as the backbone for gut or liver phospholipids, exerting downstream influence on lipid metabolism. Experiments that test this hypothesis directly by feeding triglycerides with modified structure during carefully controlled fat intake are few, particularly in humans, but their results tend to support the paradigm. Curr Opin Lipidol 12:55–60.

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Abbreviations

MCT	medium-chain triglycerides
MUFA	monounsaturated fatty acids
PL-MS	phospholipid molecular species
PUFA	polyunsaturated fatty acids
SFA	saturated fatty acids
TG-MS	triglyceride molecular species
TUFA	transunsaturated fatty acids

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Introduction

The idea that modifying the structure of dietary triglycerides, i.e. rearranging the composition or order of fatty acids on glycerol to modulate favorably the plasma lipid profile and cardiovascular health, has been discussed for many years. Although interest in the general biological application of the molecular species or structure of the triglyceride (TG-MS) continues [1,2], progress towards our understanding of their modulation of lipoprotein metabolism has been modest and was recently summarized [3]. Continuing objectives include the exploration of triglyceride structure and rates of chylomicron fatty acid hydrolysis by adipose, with the intention of establishing a TG-MS connection with the modulation of lipoprotein metabolism [4•]. The present review examines selective reports from the past 5 years to generate a rationale for the potential role of structured triglycerides in lipoprotein metabolism. At the same time, other studies are cited to exemplify design problems inherent in the implementation of experiments on this topic.

Fat absorption considerations

The original speculation that TG-MS might influence lipid metabolism was based on observed differences in fat absorption by infants fed breast milk or infant formulas that incorporated natural fats with different triglyceride orientations. Fat from breast milk and lard-based formulas with palmitic acid in the sn2 position (sn2 16:0) was better absorbed than fat with sn1,3 16:0 from palm oil [3]. Although natural triglycerides were involved, the implication was that the triglyceride structure might be important. Further speculation has been fuelled by periodic reports that the modification of triglycerides by randomizing fatty acids alters the expression of cholesterol-induced atherosclerosis in rabbits, even though lipoprotein metabolism seems to be unaffected [5].

A major impetus for TG-MS use arose with the manufacture of medium-chain triglycerides (MCT), prepared by isolating the rich supply of 8:0 and 10:0 from coconut oil and re-esterifying these medium-chain fatty acids to glycerol (hence the name 'medium-chain triglyceride'). This stable liquid preparation of medium-length saturated fatty acids was designed for clinical application of an energy-rich nutrient that would by-pass the usual lymphatic transport of fat and utilize the direct portal system in patients with fat malabsorption. The initial studies with MCT proved effective therapeutically, and revealed minimal effects on plasma lipids [6].

However, subsequent studies [7,8•,9•] in which MCT were fed at extremely high intakes (up to 40% of total energy as MCT), to the point of displacing dietary monounsaturated fatty acids (MUFA) and polyunsaturated fatty acids (PUFA), indicated that MCT can raise triglyceride and plasma cholesterol levels in hyperlipidemic [7,8•] or normolipidemic [9•] individuals. As discussed elsewhere [10], this may not represent an MCT-induced cholesterolemia so much as the displacement of diet 18:2, reflecting the extra sn2 18:2 required for phospholipids during fat absorption. The best designed of the studies [8•] indicated that only when dietary 18:2 was reduced in stages from 8%en to less than 2%en, i.e. when dietary corn oil was replaced totally by MCT, did the increase in cholesterol become significant.

Such fatty acid imbalances have been described in terms of the 18:2 threshold, wherein a specific level of 18:2 is required to protect against cholesterol elevation by saturated fatty acids (SFA) and cholesterol consumption [11]. Examples of these fatty acid relationships indicating that MCT are not necessarily cholesterolemic include studies in normolipemic women [12], patients on total parenteral nutrition [13•], and hamsters [14]. The women were fed a low 18:2 diet (3%en) that revealed MCT to be less cholesterolemic than a source of longer-chain SFA (trilaurin), whereas an interesterified mix of MCT and soybean oil (36:64) actually improved liver function tests compared with soybean oil (Intralipid) alone, and had no effect on plasma cholesterol levels [13•]. The hamster study [14] found MCT to be as cholesterol-lowering as safflower oil in a cholesterol-free diet when the intake of 18:2 was adequate at 5%en, a result reminiscent of the original human data comparing corn oil with MCT [6]. The unique structure of MCT is thus not so much the issue as the simultaneous restriction of a critical mass of unsaturated fatty acids. Furthermore, the clinical data cited in support of the cholesterol-raising nature of MCT [7,15], like the comparison in normolipemic women [12], suffer from the same shortcoming, i.e. 18:2 was lower (and below threshold) in the MCT diet period compared with the control diet. The clinically relevant point is that an adequate source of 18:2 needs to be supplied when monoacyl triglycerides and structured triglycerides such as MCT, or even carbohydrate, replace other long-chain SFA and MUFA [16•]. Likewise, a human study [17•], which introduced multiple fat changes between the baseline control diet and diets incorporating high levels of monoacyl SFA (tri 14:0, tri 16:0, or tri 18:0) without a diet control for TG-MS modification, precluded determining whether triglyceride structure was a factor in the 14:0- and 16:0-induced cholesterolemias.

The MCT and monoacyl triglyceride dependence on PUFA decribed above raises a second point implicating TG-MS in the synthesis and subsequent function of specific phospholipid molecular species (PL-MS). For example, a novel modification of MCT resulted in Caprenin, a modified triglyceride that reduces both fat absorption and alters lipoprotein metabolism. Caprenin is produced by randomly interesterifying a single insoluble long-chain SFA (caprenic acid 22:0) with 8:0 and 10:0. This combination of poorly absorbed fatty acids (22:0) with medium-length fatty acids forms a solid fat with randomly arranged short-chainlong-chain fatty acid triglyceride molecules. Although Caprenin has reduced caloric value, it also increased the LDL:HDL ratio in hypercholesterolemic men [18]. This distortion in lipoprotein metabolism presumably reflected the randomization of 8:0, 10:0, and 22:0 on the triglyceride molecule, which by extension of the argument below, could generate a sn2–22:0 phospholipid that impairs lipoprotein metabolism.

Still another entry in the low-calorie fat group of structured triglycerides was the introduction of Salatrim fats, a group incorporating 18:0 as the long-chain SFA, but interesterified with classical short-chain fatty acids, i.e. 2:0, 3:0, 4:0 [19]. Depending on the mix of the two groups of fatty acids, a hard, soft, or intermediate density low-calorie triglyceride can be formulated that reduces caloric value by virtue of poor 18:0 absorption. Salatrim at 50% of daily fat intake has a minimal impact on plasma lipids [20]. Unlike the results with 22:0 and trans18:1, the Salatrim data suggest that 18:0 in sn2 monoglyceride has a minimal impact on lipoprotein metabolism.

Phospholipid considerations

The above discourse infers that the potential benefit, or harm, to lipoprotein metabolism that might derive from the consumption of specific TG-MS may depend on certain aspects of triglyceride absorption and gut lipid synthesis. As triglyceride sn1,3 fatty acids are hydrolysed by pancreatic lipase in the gut lumen, sn2 monoglyceride forms that absorb intact, serving as the primary backbone for triglyceride synthesis in the mucosal cell [21•]. Although phospholipid synthesis in the gut is less extensive than for triglyceride and is thought to proceed via pathways involving lysophosphatidyl choline or phosphatidic acid, empirical evidence suggests that some sn2 monoglyceride from diet triglyceride may provide the backbone for gut or liver phospholipid synthesis in certain species or circumstances, especially during extensive fat absorption. Therefore, strategically (or inadvertently by interesterification) placing unique fatty acids in triglyceride sn2 could ultimately influence phospholipid structure and associated phospholipid sn2-fatty acid metabolic activity downstream, e.g. affecting acyl coenzyme A:cholesterol transferase or lecithin:cholesterol acyltransferase activity during the formation of

cholesteryl esters in the gut, liver, or plasma; release of the sn2-fatty acids from the phospholipids by phospholipase A_2 during eicosanoid metabolism; or the generation of a specific diacylglycerol from membrane phosphatidyl inositol by phospholipase C. It seems likely that nature realized the importance of this possibility, considering that the scarce PUFA in triglyceride of most saturated fats are located at sn2. Milk fat is a notable exception, with 80% of its PUFA in sn1,3 [3], which may contribute to its extraordinary cholesterolemic action.

Thus, it seems possible that both Caprenin [18], and transunsaturated fatty acids (TUFA) [22] exert their adverse effects on lipoproteins and the LDL:HDL ratio via TG-MS and the formation of atypical phospholipids. For example, HDL depression induced by TUFA may reflect the fact that impaired lecithin:cholesterol acyltransferase activity *in vitro* was found to depend on the position of TUFA or SFA in the substrate phosphatidyl choline as well as the paired fatty acid on the phospholipid molecule [23]. Thus, whereas 16:0 was inhibitory at sn2 in phosphatidyl choline, t18:1 was most inhibitory at sn2 when paired with sn1 16:0, but was more inhibitory at sn1 when paired with 20:4. Perhaps trans-18:1 is only detrimental when it becomes incorporated in phospholipids, whereas modest amounts of TUFA may have a minimal effect when metabolized as triglyceride fatty acids destined for oxidation and fail to achieve phospholipid status. The original position and shear mass of TUFA within dietary triglycerides could influence their chance of being included in phospholipids.

The clearest suggestion that diet TG-MS and PL-MS are related and exert an impact on lipoprotein metabolism derives from studies in which total fat composition and triglyceride structure were controlled in tandem via liquid formula diets. Those studies also utilized the most sensitive model systems for detecting the effects, i.e. rapidly growing piglets [24] and infants [25••]. The objective was to compare the absorption of sn2 16:0 versus sn1,3 16:0 using liquid formula diets with comparable fatty acid profiles. Surprisingly, the cholesterolemic response to 16:0 in sn1,3 (palm oil-based) in piglets was approximately 20% less (lower HDL) than the response to 16:0 at sn2 provided by a specially structured triglyceride, Betapol [24].

In the infant study [25••], breast milk (sn2 16:0 plus inherent cholesterol) was compared with a palm oil-based fat (sn1,3 16:0) or Betapol, (sn2 16:0), with all fats near 50% of total energy. The highest plasma cholesterol concentration (160 mg/dl) was found in infants fed the cholesterol-rich breast milk compared with either cholesterol-free formula (117 mg/dl), but in contrast to the pig study, the total cholesterol:HDL ratio was significantly improved by the palm oil formula, 117/62 versus 117/47 for Betapol. The infant results are interesting because the fatty acid distribution (sn2) in chylomicron triglycerides and phospholipids followed the relative dietary pattern of the two formulas, and the HDL phospholipid sn2 fatty acid positioning was reported to do the same. This supports the theory that mucosal cell phospholipid availability and subsequent incorporation into HDL tend to conserve the strategic stereospecificity found in diet TG-MS (sn2), at least when diet TG-MS are relatively homogeneous. Furthermore, PL-MS did not appear to be strictly dictated by gene-specific fatty acid allocation, but somewhat followed the 2-monoglyceride pattern from diet triglycerides.

The best of all design considerations for eliciting a TG-MS effect were thus present in the study, i.e. a test of the sn2 monoglyceride PUFA requirement; high fat intake pushing the limits on gut transport (including local gut phospholipid synthesis or availability); the use of liquid formula diets with matching fatty acid profiles but different triglyceride structure; fed to rapidly growing infants without appreciable PUFA reserves, so that diet fatty acid composition and TG-MS were extremely critical. Apparently, adding sn2 18:2 (as in palm oil) and accentuating fat transport benefited phospholipid (and HDL) pools, a favorable bias that may have been negated by the sn2 16:0 structure of Betapol. Although the contrast between piglet and infant HDL responses demonstrate the complexity of modelling human lipoprotein metabolism in animals, the infant data are reminiscent of an adult human study [26], in which a similar unique rise in HDL occurred when SFA and PUFA intake was balanced by blending palm (sn1,3 16:0), soybean, and canola oils.

On the other hand, when a palm oil versus Betapol crossover comparison was conducted in adults, in which the background dietary fat contribution was appreciable, i.e. test fats provided approximately 50% of total fatty acids, the effect of TG-MS on the total cholesterol:HDL profile was not significant at the end of the two diet periods [27]. However, the trends for lipoprotein change from the beginning to the end of each test period followed those in infants, i.e. HDL tended to rise and LDL to fall during sn1,3 16:0 intake (palm oil), and vice versa during sn2 16:0 consumption in Betapol. Similarly, as might be expected from a more acute study, in which endogenous tissue fatty acid pools would exert their bias, no postprandial differences in lipoproteins were noted after a single meal that incorporated these two fats [28].

Mass effect of polyunsaturated fatty acids

As a corollary to the above considerations, the implication is that triglyceride sn2 (especially available PUFA)

is the crux of the dietary TG-MS issue, particularly as it relates to lipoprotein metabolism. By way of example, the greatest impact of dietary triglyceride manipulation on lipoproteins is not structure specific, but rather follows the addition of PUFA-rich triglycerides to the diet. This point is related to the observation that feeding TG-MS in which appreciable sn2 PUFA are randomly or specifically displaced by SFA or TUFA can alter lipoprotein metabolism [18,22,25••]. As a consequence of these relationships, diet designs that do not exert control over total fat (fatty acid) intake, or fail to allow equilibration between diet–tissue fatty acid pools during test fat intake, reduce the chance of detecting the effects of a specific structural change linked to the fatty acid type or orientation on the triglyceride. Other examples of this point [20,29,30•] also allowed approximately 50% of the fat to derive from the background diet. In these instances, the primary focus was not on TG-MS *per se*, but rather to evaluate interesterified fats for the practical manipulation of fat delivery systems with the intention of monitoring changes in lipoprotein profiles. Such studies are not rigorous tests of TG-MS function.

In such cases and because of the restricted 'window of opportunity' associated with the PUFA mass effect, the benefit, or harm, associated with remodelling the sn2 fatty acid profile in a select number of dietary triglycerides cannot be distinguished from the simple mass effect of extraneous fatty acids (especially PUFA) contributed by the non-controlled naturally occurring triglycerides in the diet. In effect, uniquely structured TG-MS may prove most beneficial when a small dose of a specific PUFA is required for strategic insertion in the diet. However, full benefit can only be ensured when the entire fat (fatty acid) pool is provided in the form of structured triglycerides or as a specifically modified blend of natural fats, as currently occurs for parenteral nutrition [13•] or infant formulas [25••]. Ordinarily, it is easier simply to add extra PUFA-rich triglycerides as the source of the desired sn2 PUFA.

The metabolic model connotes the importance of having a strategic number of sn2 PUFA in the positive sense, as opposed to the disruptive impact of a dysfunctional fatty acid inserted in sn2 that displaces PUFA and derails lipid metabolism. Furthermore, the chance of detecting a TG-MS effect would be enhanced in a fatty acid-sensitive circumstance (e.g. rapidly growing naive infant) as opposed to a relatively insensitive system (e.g. adult human with a background of varied dietary fats). Typically, in the latter situation a specific TG-MS may provide too small a portion of the available fatty acid pool (represented by total fat intake plus tissue reserves) to alter the normal PL-MS, and so fail to exert a detectable response. That is presumably why certain experiments that have inadvertently addressed the 'flip side' of the model by inserting SFA or TUFA in sn2 [18,22] make a case for triglyceride structure. In effect, they not only limit PUFA availability but insert a 'dysfunctional' fatty acid in its place, such as 22:0 or trans18:1.

Host metabolic profile and genetic considerations

In addition to the above-mentioned caveats concerning designs that address TG-MS and lipoprotein metabolism, host-related factors (including genetic factors) affecting phospholipid synthesis or metabolism are undoubtedly important. In fact, the host metabolic profile may represent a greater consideration than the subtle dietary manipulation of triglyceride structure. For example, the evaluation of PL-MS in platelets from rhesus and cebus monkeys of similar sex, age, diet fat composition, etc. revealed strikingly inherent differences in the major pools of phosphatidyl choline molecular species, with more sn2 18:2 in rhesus and sn2 20:4 in cebus fed identical fats. Changes induced by dietary fat saturation were appreciable, but genetic differences were maintained across fat modulations [31]. In humans no sustained attempt has been made to determine the degree to which phospholipid molecular species, e.g. in HDL, vary between individuals, races, sex, age, or during metabolic stressors such as pregnancy or diabetes. The question pertains not only to pools of HDL phospholipids, but also to the PL-MS composition within the individual pools of phosphatidyl choline, phosphatidyl inositol, plasmalogens, sphingolipids, etc., and how the molecular species within each pool may respond to dietary changes in fat composition and structure.

If, indeed, the inherent differences in PL-MS in humans are large and highly variable, or if the genetic control over phospholipid synthesis far outweighs modulation by dietary fat, it may be difficult to discern effects by altering dietary TG-MS. That may explain why lipid metabolism in rats is relatively insensitive to diet fat manipulation, whereas the gerbil and cebus monkey are extremely sensitive, particularly to limitations in PUFA intake affecting SFA metabolism. The latter two species would appear to have extremely vulnerable pools of phospholipid PUFA, or something unique about their phospholipids such as genetic variants in phospholipid structure, degree of intestinal phospholipid synthesis, atypical distribution of phospholipid pools (e.g. phosphatidyl inositols, plasmalogens, sphingolipids) or possibly a wasteful, rapid turnover of precious PUFA reserves that renders the metabolism of fatty acids and lipoproteins much more responsive than in most species. Unfortunately, although we are ultimately interested in human lipoprotein metabolism, our knowledge concerning the above parameters is largely defined by studies in

the rat, admittedly a poor model for diet fat manipulation of lipoproteins.

Conclusion

An underlying rationale for experiments that probe the potential impact of dietary triglyceride structure on lipoprotein metabolism is based on a probable link between dietary fatty acids introduced in structured triglycerides that ultimately influence fatty acid stereospecificity in phospholipids. Since certain reports suggest that diet fat can modulate phospholipid structure via absorbed sn2 monoglyceride fatty acid saturation, to alter lipoprotein metabolism, it would seem prudent to further explore the specific connection between dietary TG-MS and PL-MS, particularly in the human intestinal absorptive cell, where it is seldom, if ever, assessed. Human intestinal mucosal cells may have a limited capacity for synthesizing phospholipids and apo A1 (i.e. HDL) relative to the typically studied rat intestine. Could TG-MS enhance this capacity? Do triglyceride sn2 fatty acids attain phospholipid sn2 status with any degree of certainty, or does this relationship simply represent fatty acid mass availabile for phospholipid synthesis via phosphatidic acid? A burgeoning area of concern for atherogenesis and inflammation is the impact of heated fats (oxidized lipids). Do triglyceride and phospholipid fatty acid relationships influence the outcome and is the molecular structure of either lipid class important?

From the practical point of view, it is apparent that MCT, as well as their modification by PUFA supplementation, have garnered a place in parenteral nutrition, especially when they represent the major source of daily fat calories. It is not clear whether added TG-MS will enhance MCT utilization, but it seems likely, especially if one extends the concept to PL-MS and different classes of phospholipids. More research will be required to define these limits/relationships, for example, in understanding the improved liver function tests associated with MCT(13) or the reduced caloric value of Salatrim fats(19).

With few important exceptions such as the piglet and infant studies, progress on TG-MS influence on lipoprotein metabolism has been relatively uneventful because extraneous dietary (or endogenous) PUFA compete with limited amounts of absorbed sn2-modified triglyceride. Most diet designs bear only indirectly on the issue because assessing TG-MS function was not the primary focus and only became important in retrospect. To obtain a biological effect with diet TG-MS one must be perceptive enough to measure the appropriate endpoint (e.g. lipoproteins, immune function, inflammatory response, etc.) in which altered triglyceride affecting phospholipid structure could theoretically make a difference. In addition, it is extremely critical that all the dietary fat (fatty acids) be regulated so that specific effects resulting from subtle changes in triglyceride structure might be realized.

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