Structured Triglyceride Emulsions in Parenteral Nutrition

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ABSTRACT: Over the past 3 decades, various concepts for IV fat emulsions (IVFE) have been developed. A randomized, structured-lipid emulsion based on an old technology has recently become available. This structured-lipid emulsion is produced by mixing medium-chain triglycerides and long-chain triglycerides, then allowing hydrolysis to form free fatty acids, followed by random transesterification of the fatty acids into mixed triglyceride molecules. Studies in animals have shown an improvement in nitrogen balance with the use of these lipid emulsions. Only 8 human clinical studies with these products have been performed. The results of these human clinical studies have been less promising than the animal studies; however, an improvement in nitrogen balance and lipid metabolism exceeds results associated with infusion of long-chain triglycerides (LCT) or a physical mixture of long-chain triglycerides and medium-chain triglycerides (LCT-MCT). Structured-lipid emulsion seems to induce less elevation in serum liver function values compared with standard IVFEs. In addition, structured-lipid emulsions have no detrimental effect on the reticuloendothelial system. Further studies are necessary in order to recommend the use of structured-lipid emulsions. The clinical community hopes that chemically defined structured triglycerides will make it possible to determine the distribution of specific fatty acids on a specific position on the glycerol core and therefore obtain specific activity for a specific clinical situation.

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acid deficiency and toxic effects associated with a large amount of oxidized MCT, MCT should not be used alone. MCT should, therefore, be administered with LCT. To that end, 2 approaches have been developed: physically mixing MCT vegetable oil and LCT vegetable oil or rearranging triglycerides that have both medium-chain fatty acid and long-chain fatty acid on the same glycerol molecule. The latter are structured lipids and were first developed by Babayan for PN. In European countries, both physical lipid mixtures and structured formulations are available for PN.

Due to the lipase specificity on triglyceride hydrolysis (substrate and position) and the importance of the sn position on the glycerol molecule in the metabolism of the triglycerides (absorption, incorporation in the membrane, complex lipid precursor), the concept of structured lipids appears to be very interesting in artificial nutrition. Indeed, lipolytic enzymes (lingual, gastric, and pancreatic lipases, lipoprotein lipase, and hepatic lipase) both have substrate specificity (medium-chain fatty acids are hydrolyzed faster than long-chain fatty acids) and position specificity for sn-1 and sn-3 fatty acids. Degradation of triglyceride results in the formation of sn-2 monoacylglycerol and 2 free fatty acids. The sn-2 monoacylglycerols are well incorporated in cell membrane (modulating membrane fatty acid composition) and serve as precursors of complex lipids. Sn-2 monoacylglycerols are also preferentially absorbed in intestine and are a source of reesterification by intestinal cells for resynthesis of triglycerides. On the other hand, sn-1 and sn-3 fatty acids are used for energy substrate. According to the position of the fatty acid on the glycerol backbone and the kind of fatty acid, it should be possible to deliver specific fatty acids to specific tissues in specific clinical situations by using a specific modification of triglyceride composition.

This review is mainly focused on use of IVFE with PN because structured IVFEs are currently used in clinical practice (except in North America).

**Structure and Metabolism of Structured Lipids**

Structured lipids (SLs) are defined as lipids that are modified chemically or enzymatically in order to change their structure (Figure 2). The most typical structured triacylglycerols (STG) are medium-long-medium-chain type STG (MLM-STG) having medium-chain fatty acids at the 1 and 3 positions (sn-1 and sn-3) and a long-chain fatty acid at the 2 position (sn-2; Figure 3).

SLs are produced by interesterifying medium-chain fatty acid and long-chain fatty acid on a glycerol backbone. Interesterification does not modify the nature of the native fatty acids (length, desaturation, isomerization). Chemical interesterification of fats is an old process technology for fat modification. With an initial mixture of soybean oil (for LCT) and coconut or palm oil (for MCT), structured lipids are made by first breaking down the triglycerides to form fatty acids and glycerol. These
compounds are then reesterified to form new triacylglycerols containing a randomized mixture of medium-chain fatty acids and long-chain fatty acids on their glycerol backbone. All combinations are possible (Figure 3). Only this kind of randomized SL is available in clinical practice.

Using 1,3-specific or 2-specific lipases, it is possible to synthesize 1,3-specific or 2-specific triacylglycerol called chemically STG. As explained above, chemically defined SLs could offer some advantages, depending on the kind of fatty acid and their position on glycerol backbone. For example, the choice of some fatty acids (particularly MCT) at the sn-1 or sn-3 position provides a preferential energy substrate effect with a faster hydrolysis to this STG. Incorporation of arachidonic, eicosapentaenoic acid, or very long-chain fatty acid at the sn-2 position, could provide an immunomodulating effect to this STG.

**Experimental Data in Animal Studies**

Most of the relevant studies were published 20 years ago and showed that IV STG could have beneficial effects on nitrogen balance. In these studies, randomized medium- and long-chain STG are hydrolyzed more rapidly than LCT. *In vitro*, lipoprotein lipase and hepatic lipase hydrolyzed STG slightly less rapidly than they did MCT/LCT physical mixture, but there were no differences in blood lipid parameters *in vivo*. STG appeared to be more oxidized and also decreased endogenous lipolysis. Hepatic lipid content was lower with the use of STG.

Protein metabolism and nitrogen balance have been evaluated in stressed rats (burned, septic, or injured). All of the studies showed a greater gain in body weight, a greater positive nitrogen balance, and higher albumin levels with STG compared with physical mixture or LCT. STG seems to be a better support for protein synthesis. Like MCT, STG did not affect the RES and did not increase the rate of infection. According to animal studies, randomized STG emulsions have a beneficial effect on triglyceride hydrolysis and nitrogen balance.

**Human Clinical Studies**

Eight human clinical studies with STG have been published. Six studies compared STG with LCT (1 in healthy subjects, 3 in postoperative patients, 1 in critically ill patients, and 1 in patients receiving home PN) and 2 studies compared STG with a physical mixture of MCT/LCT.

**Metabolic Pathway**

In experimental studies, STG were hydrolyzed rapidly and oxidized more fully than other IVFEs (Table 1). In these studies involving 200 patients,
Table 1

Human clinical studies evaluating STG IV lipid emulsion

<table>
<thead>
<tr>
<th>Population</th>
<th>Nutrition intake</th>
<th>Days</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STG vs LCT study</strong></td>
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<tr>
<td>Healthy subjects, n = 9</td>
<td>Part 1: (n = 6)</td>
<td>6 h</td>
<td>Lipid = 0.38 g/kg over 6 h</td>
<td>↑ Serum triglycerides, glycerol, FFA, β-hydroxybutyrate and phospholipids in all groups</td>
</tr>
<tr>
<td>Open study for parts 1 and 3</td>
<td>Part 2: (n = 8)</td>
<td>6 h</td>
<td>Lipid = 0.75 g/kg over 6 h</td>
<td>↑ Lipase activity during all infusions</td>
</tr>
<tr>
<td>Crossover study for part 2</td>
<td>Part 3: (n = 6)</td>
<td>6 h</td>
<td>Lipid = 1 g/kg over 6 h</td>
<td></td>
</tr>
<tr>
<td>Postoperative randomized, n = 10 STG and 10 LCT not malnourished</td>
<td>Lipid = 1 g/kg over 8 h</td>
<td>5–7</td>
<td>Nitrogen = 0.2 g/kg</td>
<td>No difference in liver function tests during lipid infusion in STG group: ↑ VCO₂, VO₂</td>
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<tr>
<td></td>
<td>Glucose = REE</td>
<td></td>
<td></td>
<td>REE: 29.9 ± 0.9 vs 28.2 ± 0.6 kcal/kg/d (ns)</td>
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<td></td>
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<td>↑ fat oxidation: 2.19 ± 0.24 vs 2.04 ± 0.27 g fat/kg/d (ns)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference in nitrogen balance</td>
</tr>
<tr>
<td>Postoperative randomized</td>
<td>Part 1: kcal = 80% REE</td>
<td>STG one day LCT the other day</td>
<td>Lipid = 1 g/kg/day over 8 h</td>
<td>All parts: No difference in liver function tests; no difference in lipid metabolism; no difference in nitrogen metabolism</td>
</tr>
<tr>
<td>Part 1, n = 19</td>
<td>Part 2: kcal = 120% REE</td>
<td></td>
<td>Lipid = 1.5 g/kg/day over 8 h</td>
<td>Part 2: ↑ whole body fat oxidation with STG (1.9 g/kg vs 2.4 g/kg) (p &lt; .01)</td>
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<td>Part 2, n = 18</td>
<td>Nitrogen = 0.15 g/kg/day</td>
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<td></td>
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<tr>
<td>No malnourished</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Postoperative</td>
<td>Lipid = 11.2 kcal/kg over 12 h</td>
<td>5 days</td>
<td>Nitrogen = 0.2 g/kg</td>
<td>No difference in liver function tests</td>
</tr>
<tr>
<td>n = 9 STG and 10 LCT Randomized, No malnourished</td>
<td>Glucose = 16 kcal/kg</td>
<td></td>
<td></td>
<td>No difference in serum triglycerides</td>
</tr>
<tr>
<td></td>
<td>Nitrogen = 0.2 g/kg</td>
<td></td>
<td></td>
<td>No difference in cumulative nitrogen balance and in 3-methylhistidine urinary excretion</td>
</tr>
<tr>
<td>Critically ill patients (Sepsis) randomized</td>
<td>Lipid = 1.5 g/kg/day over 12 h</td>
<td>3 or 5 days</td>
<td>Glucose provided the balance to cover REE</td>
<td>Lower ↑ in AP and bilirubin in STG group</td>
</tr>
<tr>
<td>n = 30, studied n = 20 (11 in LCT, 9 in STG)</td>
<td>Nitrogen = 0.2 g/kg/day</td>
<td></td>
<td></td>
<td>↑ Cumulative nitrogen balance in STG group: (-0.7 ± 5.9 g vs -16.7 ± 3.9 g) (p = .034)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference during 5 days or in intent to treat</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>No difference in lipid, glucose and energy metabolism</td>
</tr>
<tr>
<td>Home parenteral nutrition</td>
<td>Over 12 h</td>
<td>28 days</td>
<td>Lipid infusion rate unknown</td>
<td>No difference in plasma lipid values and plasma liver test function</td>
</tr>
<tr>
<td>Randomized, crossover study, n = 22</td>
<td></td>
<td></td>
<td></td>
<td>No difference on plasma albumin level</td>
</tr>
</tbody>
</table>

(Continued)
STG IVFE was well tolerated, and no side effects were encountered during the study periods. Hepatobiliary dysfunction frequently occurs in patients receiving PN. When patients are parenterally fed, a gradual rise in serum levels of aspartate aminotransferase, alkaline phosphatase, and bilirubin may be expected to occur after 1 or 2 weeks of PN infusion. In all of the studies performed in patients (no healthy subjects), abnormal liver function tests were observed with PN (Table 1). Nevertheless, in the STG groups, these modifications were less pronounced in 2 of 7 studies (critically ill patients and postoperative patients). In a study, 20 postoperative patients receiving PN for 5–7 days were randomized to receive either STG or LCT IVFE infused over 8 hours at a dose of 1 g/kg/day. Plasma lipid parameters (glycerol, free fatty acids, triglycerides) were not significantly different between groups. However, during lipid infusion, plasma triglyceride levels declined in both groups. During STG infusion, energy expenditure or oxidation tended to be slightly higher, but the differences were not significant (Table 1). Five additional studies comparing STG and LCT lipid emulsion also demonstrated no differences in triglyceride metabolism (plasma levels of glycerol, fatty acids, or triglycerides) or oxidation measured by indirect calorimetry (Table 1). In these studies, the rate of lipid infusion was 0.85 g/kg/day to 1.5 g/kg/day infused over 6–8 hours. However, Sandöstrom et al found that an excess of nonprotein calories (nonprotein calories = 120% BEE), 1.5 g/kg/day over 8 hours of STG was associated with a significant elevation of whole body fat oxidation (+0.5 g/kg body weight/day) in postoperative patients (p < .01). This was not observed with a hypocaloric rate and with a lower lipid infusion rate (80% of BEE and 1 g/kg/day over 8 hours; Table 1). In this former group (hypercaloric), a significant increase in glycerol, free fatty acid, and 3-hydroxybutyric acid levels was also observed. The modification of energy expenditure and whole body fat oxidation may imply that STG are more oxidized than other lipids. However, measuring fat oxidation with indirect calorimetry does not prove that it was exogenous fatty acids that were being oxidized.

A physical mixture and an STG emulsion were compared in 2 studies in postoperative patients. In a study, 25 postoperative patients receiving PN for 5 days were randomized, n = 25 [STG:12] No malnourished

To conclude, in human studies, the results of STG are conflicting. Some studies show no difference, whereas others indicate a faster clearance and a higher oxidation of STG compared with other IVFEs.

Protein Metabolism and Nitrogen Balance

Only 2 studies have evaluated the impact of IVFE on nutrition parameters such as serum levels of albumin and transthyretin. In a crossover study

<table>
<thead>
<tr>
<th>Population</th>
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<th>Days</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>STG vs MCT/LCT study</td>
<td>Calories: 100% of measured REE, glucose/lipid: 50/50 lipid infusion over 8 h n = 0.2 g/kg/day</td>
<td>5 days</td>
<td>↑ AST and ALT in LCT/MCT group ↑ Plasma triglycerides in LCT/MCT group No difference in plasma albumin and transthyretin No difference in cumulative nitrogen balance and in 3 methyl-histidine urinary excretion</td>
<td>36</td>
</tr>
<tr>
<td>Postoperative randomized, 40 included, 29 analyzed (11 in STG group) No malnourished</td>
<td>Total energy = REE + 800 kcal n = 0.2/kg/day Glucid/lipid ratio = 2/3 Lipid over 6 h</td>
<td>5 days</td>
<td>No difference in liver function tests ↑ Cumulative nitrogen balance in STG group Increase in plasma triglycerides lower in STG group</td>
<td>37</td>
</tr>
</tbody>
</table>

ALT, alanine transaminase; AST, aspartate transaminase; AP, alkaline phosphatase; FFA, free fatty acids; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; REE, resting energy expenditure; STG, structured triglyceride.
that compared STG lipid emulsion with LCT lipid emulsion in patients receiving long-term home PN (28 days), serum albumin levels were not different in the 2 periods. In our randomized study in postoperative patients, we did not find a difference in plasma transthyretin and albumin levels after 5 days of infusion of STG emulsion.

Protein metabolism was evaluated by nitrogen balance and 3-methylhistidine urinary excretion at 35 or 5 days after infusion of IVFEs36,37 (Table 1). In 20 postoperative patients receiving 0.2 g/kg/day of nitrogen, Sandstrom et al30 found no difference in nitrogen balance (nitrogen balance/day: 0.8 g in the STG group vs −0.4 g in the LCT group; Table 1). Another study compared LCT with STG using 2 infusion rates (1 g/kg/day and 1.5 g/kg/day over 8 hours) in 37 postoperative patients(Table 1), Sandstrom et al31 again found no difference in nitrogen balance in either group. However, the type of IVFE was switched every day. Under these conditions, it could be difficult to show a difference between IVFEs. In a study comparing STG with LCT in 19 postoperative patients (Table 1), Bellatone et al33 obtained a positive nitrogen balance in both groups during the first 5 days of IVFE infusion. Positive nitrogen balance was higher in the STG group, but the difference was not significant (—10.7 ± 0.5 g vs 6.7 ± 17.9 g for 5 days). In addition, there was no difference in 3-methylhistidine urinary excretion. A study comparing LCT with STG in 30 intensive care patients evaluated nitrogen balance over 3 days (Table 1). Ten of the patients in the study could not be evaluated. Patients received 0.2 g/kg/day of nitrogen. Cumulative nitrogen balance was significantly better in the STG group (9 patients; −0.7 ± 5.9 g) than in controls (—16.7 ± 3.9 g). In an intention-to-treat analysis, the difference between the groups was not significant.35

Similarly, in the 2 randomized studies that compared STG emulsion with a physical mixture in postoperative patients, the results were conflicting (Table 1).36,37 Kruimel et al37 reported a significant difference in cumulative nitrogen balance (p = .015) in favor of the STG group (—8 ± 2 g in 9 patients receiving STG) vs the physical lipid mixture (—21 ± 4 g in 10 patients). The difference became significant after the fourth day. In our study of 29 patients, neither nitrogen balance nor 3-methylhistidine urinary excretion was different at 5 days into treatment or from one day to the next.36 Nitrogen and caloric intakes were similar in both studies.36,37 A possible explanation in the results is the difference in the rate of lipid intake. In our study, 50% of calories were provided by lipid emulsion. In the Kruimel et al37 study, only 30% of calories were provided by lipid emulsion. In addition, some studies have shown that the glucose-lipid ratio is a determinant of nitrogen balance during PN infusion in the critically ill patients, with glucose being favored.40 The higher glucose intake in the Kruimel et al37 study could improve nitrogen balance and, therefore, strengthen the positive effect of STG emulsion, explaining the positive effect STG lipid emulsion had on nitrogen balance. In these studies, STG emulsion was at least as effective as other control lipid emulsions. There was a trend toward improvement of nitrogen balance and a decrease in 3-methylhistidine urinary excretion but often without statistical significance. The type of the comparative lipid emulsion did not influence the results. As urinary 3-methylhistidine excretion is the reflection of protein catabolism, these results suggest that STG could improve protein synthesis rather than decrease protein catabolism. The clinical results are in concordance with the results of animal studies. At present, the mechanism of improved protein synthesis in patients given an STG emulsion is unclear. The improvement in nitrogen balance could be explained in part by the higher oxidation rate of triglycerides and by the increase in ketone body production. However, an exogenous ketone body infusion had no beneficial effect on protein metabolism as evaluated with L[1–13C] leucine in septic patients.41

**Immunology Study**

Several recent studies have evaluated the immunologic impact of the different IVFEs on human blood cells from healthy subjects.42–46 In contrast with physical lipid mixture, LCT emulsion, or fish oil, expression of selectins, integrins, membrane surface markers for adhesion, and degranulation were not modified by STG lipid emulsion.42,43 The same observations were made with STG lipid emul-
sion concerning migration, chemotactism, adhesion and killing, the production of oxygen radicals, and the effect of lipid emulsion on cell signaling by leukocytes.\textsuperscript{44–46} It would seem that the effect of long-chain fatty acid or medium-chain fatty acid was mitigated in the presence of long-chain fatty acids within the same triglyceride molecule.

In an older experiment, the activity of the RES was studied by technetium-labeled colloid clearance.\textsuperscript{46} After 5 days of lipid administration, there was no difference between clearance before and after lipid administration, suggesting no deleterious effect of STG lipid emulsion on RES. This effect was also obtained with the MCT/LCT physical mixture.\textsuperscript{46}

**Clinical Applications of IV Structured Triglycerides**

STG lipid emulsion is at least comparable with IVFEs of LCT or MCT/LCT physical mixtures. Several studies suggest that compared with LCT or MCT/LCT mixtures, STG emulsion is more highly oxidized and may improve nitrogen balance; STG had no effect on RES and did not stimulate eicosanoid production. STG emulsion induces no more side effects than other lipid mixtures and may cause less abnormal liver function tests than other lipid products.

STG emulsion could be used as a standard lipid emulsion. However, in France, for example, the cost of this emulsion is twice that of an LCT emulsion. Under these conditions, STG emulsion should not be used as a standard emulsion. However, STG emulsion could be recommended for use in patients with liver dysfunction or hypertriglyceridemia. STG lipid emulsion could also be helpful in critically ill patients or other patients for its potential effects on nitrogen balance and immune system. Nonetheless, the clinical support for these recommendations is not strong.

Comparing a physical mixture with the current data, it is difficult to make any recommendations. Further studies are necessary before clear recommendations can be made. Such studies should evaluate and explain protein metabolism changes and evaluate endpoints such as infectious complications.

**Future Applications in Clinical Practice**

The main interest of this kind of new generation of IVFE is to use chemically defined SLs. Indeed, the distribution of fatty acids along the glycerol core could create very interesting triglycerides. Fatty acids in the \textit{sn}-1 or \textit{sn}-3 position are available for immediate energy requirements and those in the \textit{sn}-2 position are available for functional requirements.\textsuperscript{7,18} To our knowledge, no human study has been performed with this kind of lipid emulsion.

Chemically defined SLs should be developed for human use.

Nevertheless, several former animal studies have demonstrated a significant benefit of these kinds of lipids. In rat cancer models, a STG lipid emulsion containing fish oil slowed tumor growth rate without altering protein metabolism in the host.\textsuperscript{45,48} In stressed rat models, STG containing fish oil increased whole-body protein synthesis, reduced fatty infiltration in the liver, and improved the function of the RES with a reduced bacterial sequestration in the liver and the lungs.\textsuperscript{47,48} More recently, Simoens et al\textsuperscript{52} evaluated plasma lipid levels, the distribution of exogenous fatty acids in plasma and tissue lipids in STG molecules with medium-chain fatty acid on \textit{sn}-1 and \textit{sn}-3 positions, and a long-chain fatty acid on \textit{sn}-2 position in dogs receiving high-fat PN (lipid providing 55% of calories) over a 4-week period.\textsuperscript{49} The triglycerides and phospholipids from this new emulsion were more efficiently metabolized. However, fatty acid distribution in hepatic and extrahepatic tissues was not different.

**Conclusion**

In conclusion, randomized STG lipid emulsion (MCT-LCT) is as effective for calories and nitrogen balance as other lipid emulsions. Several studies have demonstrated a trend toward improved hydrolysis and nitrogen balance. However, there have been no clinical studies evaluating the primary clinical endpoints such as infectious complications, morbidity, length of stay, etc. However, the real interest of STG is chemically defined STG. Research and manufacturer laboratories should develop these kinds of structured triglycerides, which could modify the clinical endpoints in specific clinical situations.

**References**


36. Gollaher CJ, Fehner K, Karlstad M, Babayan VK, Bistrian BR. The effect of increasing levels of fish oil-containing structured triglycerides.
