Original Paper

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Influence of Different Fat Emulsions with 10 or 20% MCT/LCT or LCT on Lipoproteins in Plasma of Patients after Abdominal Surgery

Abstract

In patients after elective abdominal surgery, different fat emulsions were used to compare their efficacy in total parenteral nutrition and in normalizing plasma lipoprotein levels. In five different groups with 5 patients each, half of the nonprotein calories were given as medium-chain triglycerides/long-chain triglycerides (1:1) or as long-chain triglycerides alone in 10 or 20% fat emulsions or as glucose alone in a control group for 7 days. After surgery, an initial decrease of all plasma lipoprotein components was followed by a different behavior of glyceride-glycerol, cholesterol, phospholipids, and apolipoproteins. Glyceride-glycerol in very-low-density lipoproteins and high-density lipoproteins is increasing during infusion of fat emulsions and decreasing during overnight interruption of infusions. After the 7-day infusion period, there was no significant difference in very-low-density lipoprotein glyceride-glycerol as compared with the values before different infusions. Low-density lipoprotein cholesterol is reaching and exceeding preoperative concentrations between the 4th and the 7th day, most during infusion of 10% fat emulsion and especially due to an increase of free cholesterol. High-density lipoprotein cholesterol and apolipoprotein A-I reach preoperative levels during infusion of fat emulsions but not with glucose alone. Higher than preoperative values are reached in phospholipids with all fat infusions already on day 4. Abnormal lipoprotein X occurred least with the medium-chain/long-chain triglyceride 20% fat-infusion. This fat emulsion is suggested as having the best normalizing effect on plasma lipoproteins and best tolerance in patients after surgery.

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Introduction

Fat emulsions are well established in total parenteral nutrition (TPN). Besides soybean oil emulsions containing only long-chain triglycerides (LCT), since several years medium-chain triglycerides (MCT) in a 1:1 mixture with LCT are applied. They supply both MCT as fast-energy source as well as the essential long-chain fatty acids [1, 2]. Fat emulsions are available with 10 and 20% triglyceride. In surgical or intensive care patients the lipoprotein metabolism is deranged due to the effect of catecholamines and additional insulin resistance [3, 4]. A drastic decrease in low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterols and apolipoproteins is observed. TPN is necessary to supply energy and essential nutrients for at least several days. As fat emulsions contain mainly triglycerides and phospholipids but not apolipoproteins, endogenous lipoproteins are modified strongly in the sense of an enrichment with infused components, an exchange of lipoprotein components between density classes [5], and the development of Lp-X-like particles in plasma. Originally Lp X is known as a pathological plasma lipoprotein rich in phospholipid and free cholesterol and produced in obstructive jaundice. Lp-X-like particles after fat infusion can be interpreted as the consequence of infusion of fat emulsions with imbalanced composition. Most studies are performed with short-time infusions, and the effects of both triglycerides and their emulsifiers have not been characterized sufficiently either in volunteers [5] or in different groups of patients during several days [5, 6]. The aim of this study was to compare the effect of infusion of fat emulsions with 10 or 20% MCT/LCT or LCT alone for 1 week on plasma lipoprotein concentration and composition after elective surgery in order to find out the fat emulsion with the best normalizing effect on the deranged lipoprotein metabolism in patients after surgery.

Patients and Methods

Five groups of patients were randomized after colon resection (5 normolipemic men or women each, 30–70 years old, body weight according to Brocal index < +20%). No considerable postoperative complications were observed. TPN was performed with 1.5 g amino acid/kg body weight/day and as nonprotein calories glucose alone or glucose 20% in combination with fat (1+1). Energy supply was calculated as 1.5 times resting energy expenditure according to the Harris-Benedict formula [7]. The five groups received glucose alone or glucose plus LCT 10 or 20% emulsions (Intralipid® 10 or 20%) or glucose plus MCT/LCT 10 or 20% (Lipofundin MCT/LCT® 10 or 20%), respectively. TPN was infused continously, but the fat emulsions were given every day from 08.00 to 24.00 h. Preoperative blood samples were drawn 10 h after the last nutrient supply. Blood samples were also taken on days 1, 4, and 7 after surgery. Venipuncture was performed on each of these days before and after 16 h of infusion of glucose or glucose and fat emulsions. Informed consent was received, and the study protocol was approved by the Ethic Committee of the Medical Faculty of the University of Munich.

Very-low-density lipoprotein (VLDL) and LDL were separated by ultracentrifugation in a Beckman Ti 50 rotor [8], with the LDL bottom fraction representing HDL. In lipoprotein fractions triglycerides (TG) were determined by an enzymatic colorimetric method (kit No. 701 912) and expressed as glyceride-glycerol (GG) because of the different molecular weights of MCT and LCT. As confirmed by controls, free glycerol contributed less than 5% to total glycerol in lipoprotein fractions. Total cholesterol (CH) was determined by kit No. 236 691, free cholesterol (FC) by kit No. 310 328, esterified cholesterol (CE) was calculated as difference of total and FC. Phospholipids (PL) were measured colorimetrically by kit No. 124974 (all Boehringer Mannheim, Germany). Apolipoprotein A-I (apo A-I) was determined in HDL and apolipoprotein B (apo B) in VLDL and LDL by nephelometry [9], VLDL-apo B determination was done after lipase treatment (1 U/μl) of triglycerides in the sample [10]. Antisera and standards were purchased from Immuno (Heidelberg, Germany) and Behringwerke (Marburg, Germany). Values are given as mean ± SD. Plasma was tested for Lp X according

Table 1. GG (mmol/l; mean ± SD) in VLDL before surgery and 1, 5, and 7 days before (a) and after (b) 16-hour infusion of either glucose, LCT 10%, LCT 20%, MCT/LCT 10%, or MCT/LCT 20% (n = 25, 5 patients in each group)

Group	Time, days						
	−1 (pre-operative)	+1		+4		+7	
		a	b	a	b	a	b
Glucose	0.84±0.58	0.40±0.24	0.34±0.25	0.47±0.32	0.35±0.20	0.91±0.64	0.83±0.54
LCT							
10%	0.54±0.20	0.23±0.13	0.82±0.25	0.31±0.16	0.99±0.23	0.50±0.24	1.31±0.47
20%	0.53±0.36	0.31±0.13	0.59±0.31	0.49±0.10	0.91±0.54	0.63±0.38	1.00±0.35
MCT/LCT							
10%	0.75±0.23	0.34±0.09	0.69±0.22	0.46±0.12	1.03±0.27	0.58±0.35	0.82±0.43
20%	0.79±0.38	0.47±0.36	1.56±0.74	0.74±0.24	1.58±0.55	0.74±0.38	1.14±0.43

All values after lipid infusion are significantly different.

to Seidel et al. [11]. The distribution of core and surface components in lipoprotein particles was calculated by the ratio of CE + TG/FC + PL + apo A-I in HDL or apo B in VLDL and LDL. Statistics were tested with the SPSS PC 4.0 program. The analysis of variance was performed by Anova, the significance of factors was tested by the F test, comparison of group mean values was made by using the Student-Newman-Keuls test (p < 0.05).

Results

There are no significant differences in plasma lipid concentrations between the groups before surgery and before fat infusions (table 1; fig. 1–3). After surgery, all components of the plasma lipoprotein fractions VLDL, LDL, and HDL decreased, most pronounced in LDL and HDL. Pre- and postoperative fasting VLDL GG values were not significantly different. Preoperative fasting levels of GG were reached again on day 7 in the fasting state by the groups with glucose and LCT 20%, but the GG values of the other groups were also remarkably increased. There were

no statistically significant differences between the GG concentrations of the groups before any infusion on day 7. In the groups with fat, the GG concentrations after infusion exceeded in every case fasting concentrations (table 1). Infusion of MCT/LCT 20% emulsion resulted on the 4th day in the highest increase of GG in VLDL, with 1.58 mmol/l on the average, but the levels remained still in the normal range. GG in HDL was at the same time 0.91 mmol/l (not shown). The overnight fat elimination of this emulsion was as adequate as that of the other emulsions. In the HDL fraction MCT-containing emulsions created higher GG values. In LDL an initial decrease of GG on the 1st day due to surgery was followed by a gradual increase of values before and after all infusion regimens until the 7th day (not shown).

CH decreased after surgery by nearly 50% in all lipoprotein fractions and increased significantly (p < 0.05) in LDL before all fat infusions at day 7 (fig. 1). Treatment with MCT/LCT 10% emulsion induced highest CH con-
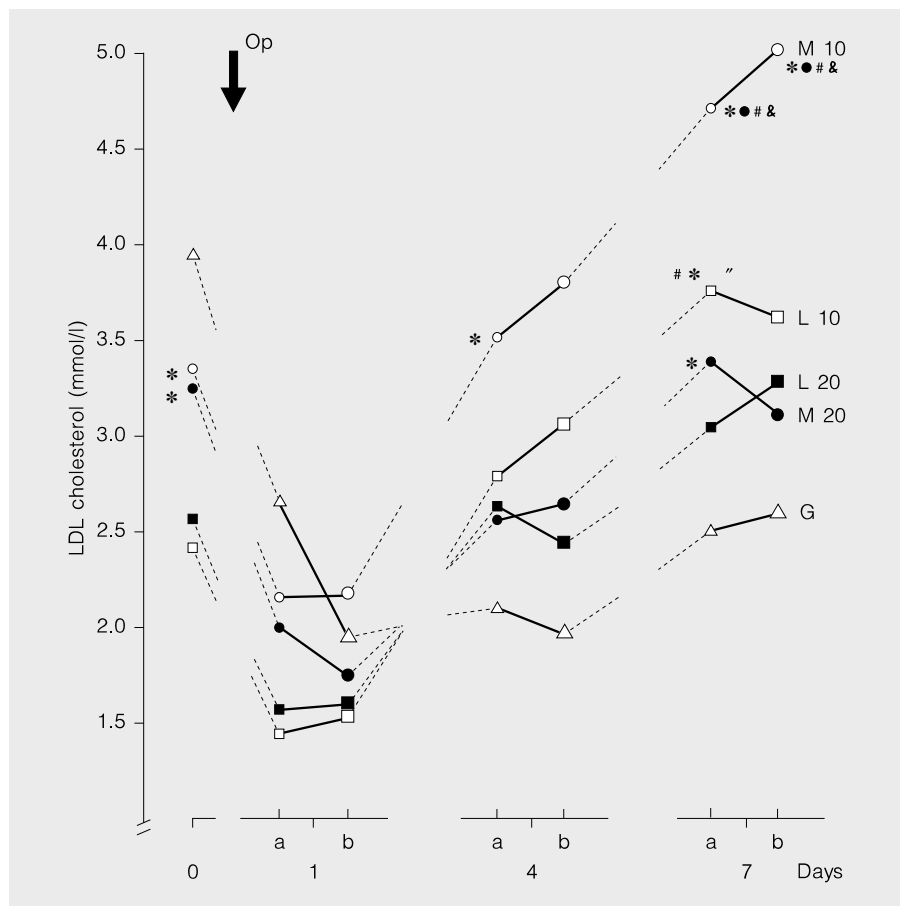
Fig. 1. Cholesterol in LDL before surgery and 1, 4, and 7 days afterwards, before (a) and after (b) 16-hour infusion of either glucose (G), LCT 10% (L10), MCT/ LCT 10% (M10), LCT 20% (L20), or MCT/LCT 20% (M20; n = 25, 5 patients in each group). On day 7 before infusion all LDL cholesterol concentrations were significantly higher than on the 1st day after surgery. Significant differences of the mean values of different fat infusions are only shown on day 7. Significant differences of the mean values within one infusion regimen are shown only for before infusion values. The signs on the right of the mean values indicate significance of differences between infusion regimens: MCT/LCT 10% vs. LCT 10% (*), vs. LCT 20% (●), vs. MCT/LCT 20% (#), vs. glucose (&) (p < 0.05); ″ indicates significant difference between LCT 10% and glucose. On the left side * indicates differences from the 1st postoperative day. During MCT/LCT 10% infusion # indicates significant differences from all other values before infusion and from preoperative values; during LCT 10% # indicates significant difference from preoperative value and the 1st postoperative day.

centrations in VLDL, LDL, and HDL. On the 7th day, the LDL CH concentrations differed significantly during MCT/LCT 10% infusion from all other groups with fat infusion, LCT 10% only from glucose (fig. 1). With glucose alone postoperative LDL CH was still significantly lower on day 4 and not reestablished even on day 7. The preoperative HDL CH concentrations were restored only with fat emulsions (not shown).
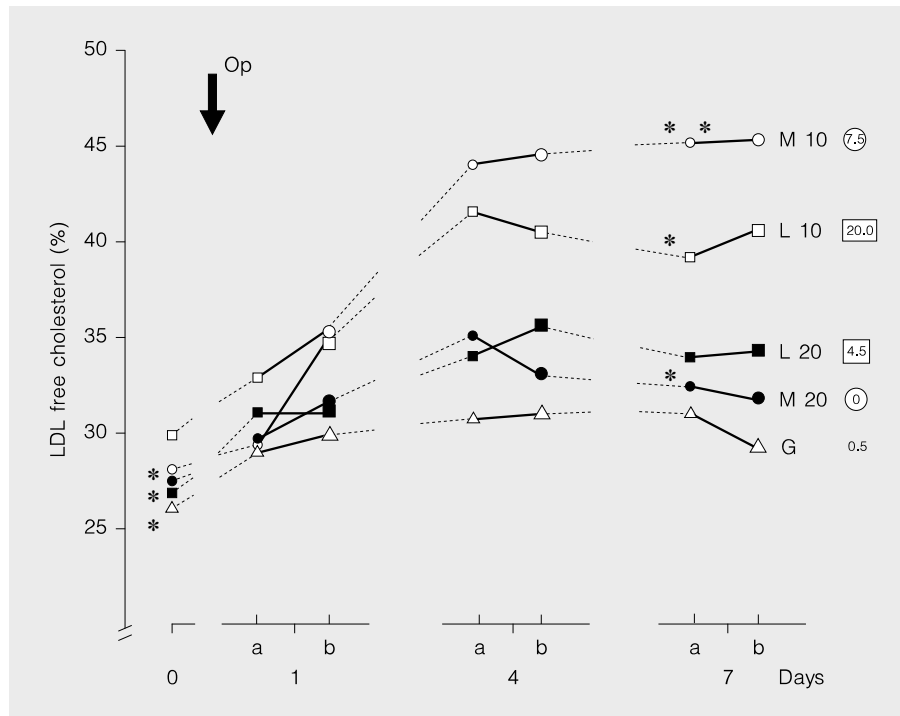
Fig. 2. FC in LDL before surgery and 1, 4, and 7 days afterwards, before (a) and after (b) a 16-hour infusion of either glucose (G), LCT 10% (L10), MCT/LCT 10% (M10), LCT 20% (L20), or MCT/LCT 20% (M20; n = 25, 5 patients in each group). Significant differences of the mean values of different infusion regimens are only shown an day 7 (p < 0.05). On the right of the mean values * indicate significant difference from the glucose regimen. Significant differences of mean values within infusion regimens are shown only for values before the infusion: on the left side * indicate significant differences from 1st postoperative day. The numbers on the right mean frequencies of samples positive for Lp X.

FC and CE both decreased after surgery and increased during the week of parenteral fat infusion. However, there were different effects of the fat emulsions. The much higher increase of LDL CH during infusion of the 10% than of the 20% fat emulsions was due to an increase of FC (fig. 2). As a consequence the percentage of CE of total CH in LDL decreased from normal values above 70% before surgery to 61% after 7 days of LCT 10% infusion and to 55% after MCT/LCT 10% infusion, whereas with 20% fat emulsions the CE percentage did not decrease below 65%.

The test for Lp X was always positive during LCT 10% after the 4th day (frequency 20 in 5 patients on days 4 and 7; fig. 2), incidently positive during MCT/LCT 10% (frequency 7.5), but only slightly positive during LCT 20% (frequency 4.5), and completely negative during MCT/LCT 20% and during glucose infusion (fig. 2). The percentage of CE of total CH in HDL remained constant immediately after surgery as well as after 7 days with fat infusion (not shown).

PL also decreased significantly after surgery, most in LDL and least in VLDL. After
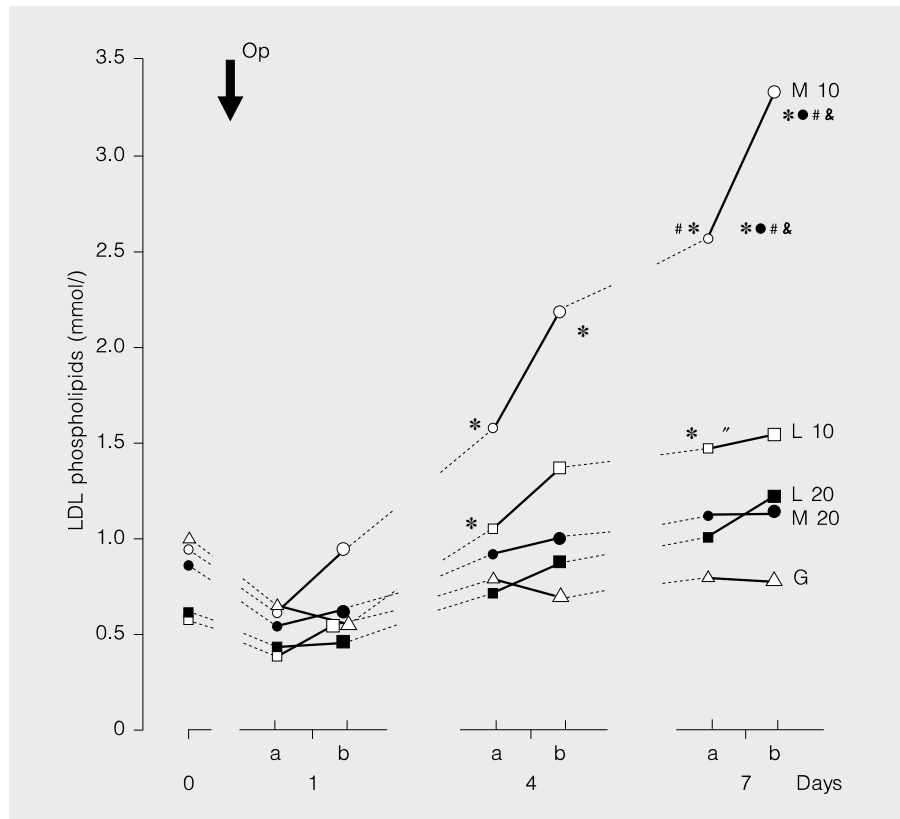
Fig. 3. PL in LDL before surgery and 1, 4, and 7 days afterwards, before (a) and after (b) a 16-hour infusion of either glucose (G), LCT 10% (L10), MCT/LCT 10% (M10), LCT 20% (L20), or MCT/LCT (M20; n = 25, 5 patients in each group). Significant differences of the mean values of different infusion regimens are only shown on day 7 (p < 0.05). Significant differences of the mean values within one fat infusion regimen are shown only for values before the infusion. Signs on the right indicate significant differences between infusions: MCT/LCT 10% vs. LCT 10% (*), vs. LCT 20% (●), vs. MCT/LCT 20% (#), vs. glucose (&); " indicates significant difference of LCT 10% vs. glucose. On the left side * indicate significant difference from the 1st postoperative day; * indicates significant difference in comparison to day 4.

1 week of TPN, the preoperative HDL PL concentrations were not reached again with glucose, however, exceeded preoperative values with fat emulsions. PL in VLDL and HDL behaved similar during all fat infusions (not shown). The LDL PL concentrations before infusion were on the 7th day with 10% fat emulsions significantly higher than before surgery (fig. 3). This is not the case during treatment with 20% fat emulsions. MCT/LCT 10% emulsions created by far the highest concentrations of PL in LDL before and after infusions. The PL concentrations during infusion of LCT 10% differed significantly from glucose infusion (fig. 3).

Apo A-I and B decreased significantly in all lipoprotein fractions after surgery. LDL-apo B reached preoperative concentrations within
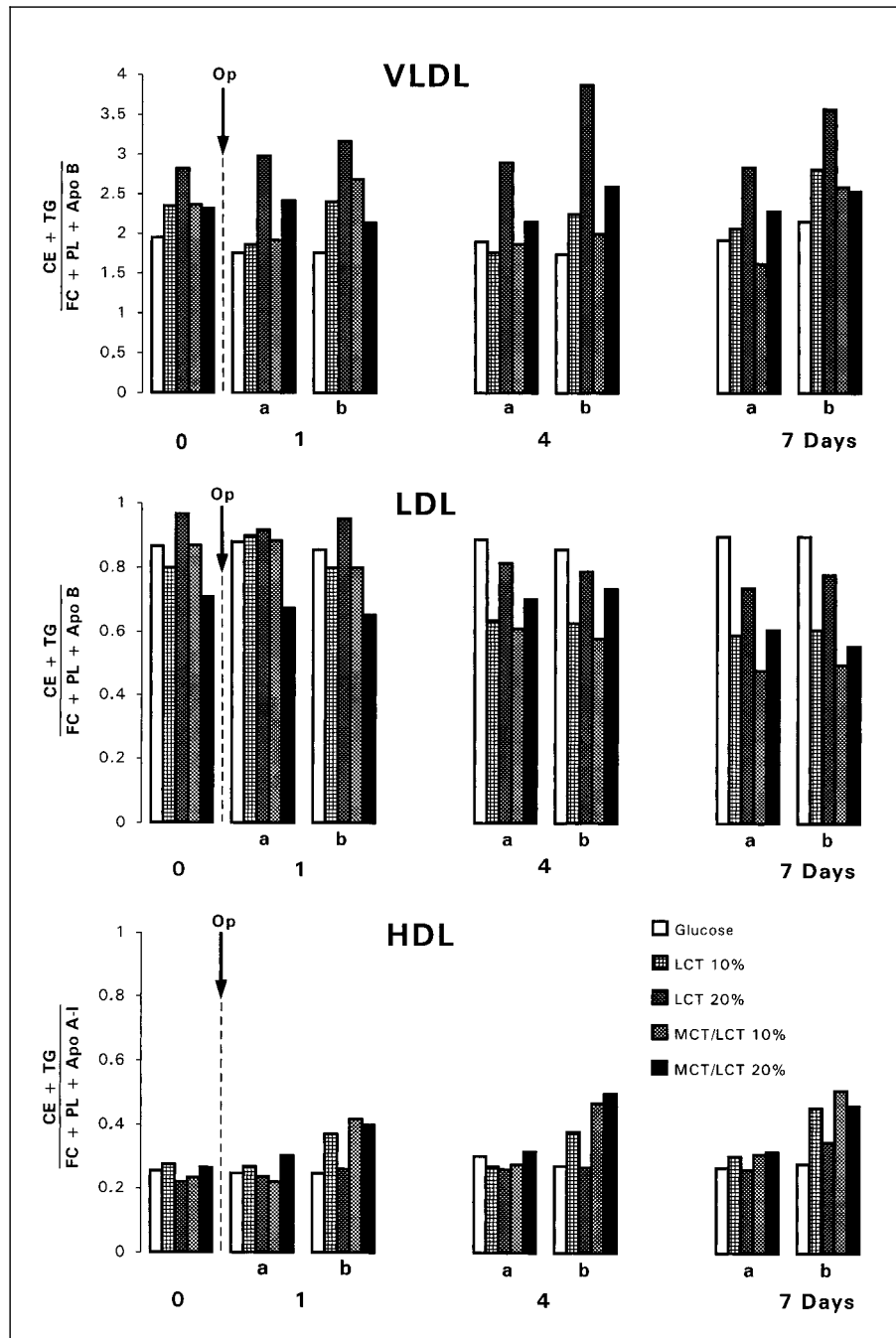
Fig. 4. Ratio of surface (CE+TG) and core (FC+PL+apo B or Apo A-I) components in VLDL, LDL, and HDL before surgery and 1, 4, and 7 days afterwards, before (a) and after (b) 16-hour infusion of either glucose, LCT 10%, MCT/LCT 10%, LCT 20%, and MCT/LCT 20% (n = 25, 5 patients in each group).

the study period only with fat infusions, but not during infusion of glucose alone. LCT 20% infusions resulted in higher apo A-I values in HDL and MCT/LCT 20% in higher apo B values in VLDL than the other lipid emulsions on day 4 (not shown).

The composition of lipoproteins is described more in detail by the ratio of core components (CE, TG) to surface components (FC, PL, apolipoproteins). With glucose infusion this ratio did not change in any lipoprotein fraction during the study. Fat emulsions affect the ratio of core and surface components in different ways (fig. 4). In VLDL the ratio was increased by 20% fat emulsions, with LCT more than with MCT/LCT (fig. 4). After infusion of 10% fat emulsions the increase of this ratio was much smaller. In LDL the ratio decreased, especially with MCT-containing fat emulsions; the differences were, however, not significant. In HDL, immediately after the infusion of MCT-containing fat emulsions, the increase of the ratio exceeded regularly that after the LCT infusions, starting on the 1st postoperative day. These differences were equalized regularly at the end of the interrruption periods of 8 h.

Discussion

In the catabolic situation after surgery or trauma, plasma lipoproteins are deranged [12, 13]. The use of fat emulsions in TPN of these patients will improve nutrition and enhance normalization of serum lipoproteins towards values before surgery [14]. As a source of energy MCT are superior to LCT due to their faster elimination and preferential oxidation [1, 15]. It was the purpose of this study to compare the effects on plasma lipoproteins of LCT and MCT/LCT in 10 or 20% fat emulsions and glucose alone as nonprotein calories. The amount and natural

source of the emulsifier egg phospholipid was the same in all fat emulsions. In the 20% fat emulsions the ratio TG/PL was increased by doubling the TG content. With 7 postoperative days, this study observed a longer period than other studies before [16, 17]. Morning VLDL GG concentrations in the group with infusion of glucose alone as nonprotein calories are the consequence of endogenous TG synthesis. During fat infusion, the endogenous VLDL lipoproteins are mixed with exogenous TG/PL particles which caused remarkable increases of GG in lipoprotein fraction d <1.006. During 8 h overnight interruption of infusion, however, GG decreased again. As we already could show, all lipoprotein fractions are influenced by fat infusions [18].

In this study, the course of HDL TG is similar to that of VLDL TG, indicating the mutual influence on VLDL and HDL during metabolism of exogenous TG. In VLDL the GG values of day 4 after 8 h interruption of MCT/LCT infusions were higher than at the end of the LCT infusion (table 1). This is in part due to the higher amount of MCT than LCT which are infused in the same volume of infusion. On the other side, MCT are cleaved faster than LCT [18]. MCT may even restrict the LCT elimination rate by displacing LCT from the surface of particles [19]. In contrast to the variation of VLDL GG, there was a continuous increase of LDL GG values after overnight interruption of all infusions on days 1–4 which did not return to preinfusion values (not shown). This indicates, that the LDL fraction probably contains TG of endogenous origin or with longer duration. The highest GG concentrations in LDL were in both MCT/LCT groups. This result is only in part explained by higher but not significantly elevated initial values in these patients as compared with the other groups before surgery. From in vitro experiments a greater MCT

than LCT accumulation at the LDL phospholipid surface is known [20]. There is obviously a net transfer of MCT from emulsions to LDL augmented by cholesteryl ester transfer protein activity [5, 18, 21]. This was also demonstrated by changes of the TG fatty acid patterns [22].

The CH concentrations in VLDL, LDL, and HDL were normalized within 7 days after surgery only by using fat infusions. The amount of cholesterol which was infused with the fat emulsions was derived from egg phospholipid emulsifier. Even if the PL and CH contents in the 10% emulsions were higher, the absolute amount of CH is too small to explain the increase of VLDL and LDL CH during MCT/LCT 10% infusion to higher values than before surgery (fig. 1). A CH transfer from other lipoprotein fractions is thought to be in similar ranges during the infusion of the different fat emulsions with the same cholesterol content [5]. Because of the increase of FC, a relative deficiency of lecithin-cholesterol acyltransferase after surgery can be assumed. Possibly but improbably other sources of FC could be the release from endothelial cells or enhanced CH synthesis by the liver. The origin of this FC is still uncertain, but a higher increase in plasma FC was also observed during infusion of LCT 10% emulsions in comparison to 20% [23] and in HDL during MCT/LCT infusion in comparison to LCT [24]. In volunteers FC increases in VLDL and LDL in connection with a higher CE transport from HDL to exogenous particles during LCT infusion in comparison to MCT/LCT infusion [17]. In another study with a 10% LCT emulsion an 43% increase of FC in plasma was accompanied by a 16.5% reduction of CE in HDL [25]. In vitro experiments show a greater depletion of LDL cholesteryl esters during incubation with MCT than with LCT due to cholesteryl ester transfer protein activity in ex-

change with triacyl accumulation [21]. The excess amount of PL in 10% fat emulsions probably leads to mesophases of particles enclosing cholesterol which float during ultracentrifugation with LDL particles at density d = 1.063 [26]. This interpretation of the increase of FC is supported by similar results of PL in LDL during MCT/LCT 10% infusion (fig. 3). The fact that MCT/LCT 10% is producing much higher LDL PL values than the LCT 10% emulsion supports a special role of MCT when artificial fat particles are mixed with endogenous LDL, as demonstrated earlier [5].

The decrease of plasma apolipoproteins after surgery was of similar extent as that of lipids. The increase of apo B in VLDL during TPN was faster during parenteral nutrition with fat than without. Preoperative LDL apo B and HDL apo A-I concentrations were not reached within 7 days with glucose alone, indicating the risk of development of a fatty liver during nutrition with carbohydrates alone as energy source, because of the lack of structure protein for the lipoproteins to be secreted from the liver.

The appearance of an Lp-X-like lipoprotein may be seen in connection with high concentrations of PL and FC. This abnormal lipoprotein is characterized by high PL and FC contents [27]. It is suggested to arise from PL supplied by fat emulsion and to leach FC associated with membranes. The Lp-X-like particle is cleared very slowly from plasma [28, 29]. Our findings correspond with results where in only 6 of 23 patients Lp X was detectable after 5 days of the infusion of Intralipid 20% [30].

Information about the composition of lipoproteins can be drawn from the ratio of components. The change of a ratio is due either to enrichment of particles with an infused component, i.e., TG and PL, or to lipoproteins combined with newly secreted or transferred

apolipoproteins. Therefore, the altered ratio of core and surface components in the lipoprotein fractions gives evidence of changes of one or more components. Increasing PL concentrations during the infusion of fat emulsions and elevated levels of FC together with postoperatively again increasing apo B levels, which turn back to preoperative values, are the explanation for the decreasing ration in LDL. Thereby the higher amount of PL in the 10% emulsions in comparison to the 20% emulsion leads to lower ratios of core and surface components. High TG concentrations during the infusion of fat emulsions are the explanation for increasing ratios in VLDL and HDL, whereby the 20% fat emulsions and LCT cause higher ratios than 10% fat emulsions and MCT (fig. 4). Concomitantly the infusion of fat emulsions influences the size and distribution of HDL particles [31].

This study with patients after abdominal surgery clearly demonstrates advantages of a balanced fat-containing TPN system regarding alterations in fat and lipoprotein metabolism. Comparing different fat emulsions. MCT/LCT-containing 20% fat emulsions are altogether more efficient with respect to restoration of preoperative lipoprotein concentrations, i.e., LDL cholesterol, LDL free cholesterol, LDL phospholipids (fig. 1–3), and composition (fig. 4) as well as avoidance of formation of Lp X (fig. 2). The advantages of MCT/LCT fat emulsion were demonstrated also by means of other blood parameters such as free fatty acids and their elimination [32] and by measurement of oxidation with ^{13}C-labeled MCT [1].

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