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Successful Treatment of Severe Hypertriglyceridemia with a Formula Diet Rich in Omega–3 Fatty Acids and Medium-Chain Triglycerides

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Abstract
Background: Patients with highly increased plasma triglyceride levels are at risk of developing serious complications such as pancreatitis, coronary heart disease and stroke. Therefore it is important to rapidly decrease plasma triglyceride levels. A sufficient control of triglyceride levels with drugs like fibrates, statins or nicotinic acid can usually only be attained after a couple of weeks. Plasma exchange appears to be a fast but expensive method to reduce triglyceride levels. In this study we describe the use of a new ω–3 fatty acid and medium-chain triglyceride-rich formula diet as a therapeutic concept to reduce plasma triglyceride levels fast and effectively. ***Methods:*** Thirty-two patients with severe hypertriglyceridemia were treated with the especially composed formula diet for a period of 7 days. ***Results:*** Within this period of time, plasma triglycerides decreased from 1,601 (402–4,555) to 554 (142–2,382) mg/dl ($p < 0.05$). Total cholesterol levels were reduced from 417 (211–841) to 287 (165–457) mg/dl ($p < 0.001$). Fasting glucose and uric acid levels also slightly decreased (–8%; –12%). The formula diet as a 1-week treatment was well tolerated and accepted by the patients. ***Conclusion:*** This diet was successfully used as an acute treatment in severe hypertriglyceridemia and showed effectiveness in rapidly and safely lowering plasma triglyceride levels.

Introduction

Severe hypertriglyceridemia (SHTG) is associated with pancreatitis and symptoms of hyperviscosity [1, 2]. The role of elevated triglyceride (TG) levels in the development of cardiovascular disease is discussed controversially. Postprandial hypertriglyceridemia seems to be an important risk factor for the development of coronary heart disease (CHD) [3–8]. Recently the extensive epidemiological assessment by Sarwar et al. [7] showed a strong association between TG concentrations and the risk of CHD. To support these findings the report from the prospective Copenhagen City Heart Study [8] indicated that highly elevated non-fasting TG values (>450 mg/dl) were predictive of CHD events in a large general population cohort of 14,000 men and women.

SHTG is generally characterized by TG levels of >750 mg/dl. It is difficult to decrease plasma TG levels to the normal range in a relatively short period of time. Drug treatment combined with a low-fat diet does not lead to satisfactory results within a short period of time [9, 10].

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Table 1. Composition of the formula diet

Energy per ml	1 kcal	
Protein	15% of total energy (75 g/2,000 ml)	Sodium caseinate
Carbohydrate	36% of total energy (178 g/2,000 ml)	Maltodextrin
Fat	49% of total energy (110 g/2,000 ml)	MCT oil, soybean oil, fish oil, egg lecithin
MCT	35% of total energy (77g/2,000 ml)	
LCT	9% of total energy (20 g/2,000 ml)	Non-fish oil LCT
ω–3 fatty acids (EPA + DHA)	5% of total energy (12 g/2,000 ml)	
Vitamin E (DL-α-tocopherol)	0.234 g/2,000 ml	
Vitamins, minerals, trace elements	According to international nutritional recommendations	

Sometimes even plasma exchange has to be performed in order to rapidly lower TG levels.

The liver cell is equipped with two independent but interacting systems of fatty acid (FA) oxidation: the mitochondrial and the peroxisomal systems. While the mitochondrial system mainly processes medium- and relatively short long-chain FAs, very long-chain unsaturated FAs (>18–20 C atoms chain length) are degraded mainly by the peroxisomal system. Apparently, these two systems cooperate as far as the peroxisomal system first cuts the very long-chain FAs down to a chain length of 10–12 C atoms. The further breakdown of thus generated medium-chain FAs is then accomplished by the microsomal system. Regarding a therapeutic approach to an optimized FA oxidation system of the liver it would seem obvious to separately stimulate the two FA oxidation systems in order to maximize their cooperation.

The natural way to accomplish this would be to cause gene induction of the respective enzymatic cascades by offering a very high concentration of the respective substrate FAs. As has been shown by experiments on the cellular and subcellular level, the ideal substrate for gene induction of the mitochondrial FA oxidation system are medium-chain FAs (C-8, octanoate, and C-10, decanoate). The peroxisomal FA oxidation system is optimally induced by very long-chain ω–3 FA (eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA).

Dietary medium-chain TGs (MCT) have thus been used in order to avoid the postprandial rise of plasma TGs due to chylomicron formation and release [11]. ω–3 FAs from fish oil were also shown to have the capacity of lowering plasma TG levels [12–14]. The American Food and Drug Administration has approved ω–3 FAs for the treatment of SHTG [15]. Furthermore it is known that fish oil capsules can safely be combined with other medications in the treatment of SHTG [16].

We therefore designed a formula diet which is rich in ω–3 FA and MCT in order to investigate its potential use in patients with SHTG. The purpose of this formula diet was to reduce severely increased TG levels within a very short period of time and thus have an acute treatment for SHTG.

Materials and Methods

Composition of the Formula Diet

The diet contained MCT oil as the main energy source, ω–3 FAs (EPA and DHA) and protein. Vitamins, minerals and trace elements were added according to international nutritional recommendations. A low carbohydrate content was accomplished. Long-chain TGs of >12 C (except EPA and DHA) were avoided as far as possible. The composition of the formula diet is described in table 1. One milliliter of the formula contained 1 kcal, protein content was 15% of the total energy derived by sodium caseinate. Carbohydrate content was lowered to 36% of the total energy, the carbohydrate source was maltodextrin. The total fat content of 49% of the total energy consisted of MCT oil (35% of the total energy), soybean oil (long-chain TG: 9% of the total energy), fish oil (EPA + DHA: 5% of the total energy) and egg lecithin.

The patients consumed between 1,500 and 2,000 ml formula diet/day. Additionally sugar-free and very low-fat foods like plain bread or vegetables were allowed.

Patients

Thirty-two patients (15 males, 17 females) with SHTG (TG >750 mg/dl fasting) who had been referred to the outpatient clinic of our university for treatment were included in this study. Mean age was 38.7 (range 18–67) years. Mean BMI was 25.4 (range 19.5–31.0). Four of the patients (3 males, 1 females) suffered from type 2 diabetes mellitus. Two patients (1 male, 1 female) had a history of hyperlipidemic pancreatitis. All patients were untreated at the time of their first clinical visit as part of the inclusion criteria.

Informed consent was given by all patients. All procedures complied with the Helsinki Declaration. The study protocol was approved by the local ethical committee of the university.

Table 2. Statistical data concerning the plasma contents of triglycerides, phospholipids, total cholesterol, free cholesterol and esterified cholesterol, glucose and uric acid in patients with severe hypertriglyceridemia receiving the formula diet for a period of 7 days

	Triglycerides mg/dl	Phospholipids mg/dl	Total cholesterol, mg/dl	Free cholesterol, mg/dl	Esterified cholesterol, mg/dl	Glucose mg/dl	Uric acid mg/dl
Day 1							
Mean	1,601	485	417	237	200	167	6.93
SD	1,061	223	190	194	80	77	2.34
Min	402	22	211	45	21	83	4.00
Max	4,555	1,000	841	780	361	366	11.80
Day 7							
Mean	554	323	287	95	190	154	6.08
SD	481	108	96	54	49	56	2.11
Min	142	181	165	38	126	82	3.30
Max	2,382	605	457	223	327	313	11.00
p value	0.02	<0.01	<0.01	<0.01	<0.01	n.s.	n.s.

Study Protocol

The patients were given 1,500–2,000 ml of the formula diet for 7 days. Laboratory and clinical data were compiled before the beginning of treatment (day 1) and at the end of treatment (day 7).

During the clinic visits on days 1 and 7, blood samples were taken for analysis of fasting glucose, uric acid, TGs, and total cholesterol.

Laboratory Methods

By ultracentrifugation of the plasma (Beckman Coulter, Rotor 50.3 Ti), the isolation of chylomicrons, very low-density lipoprotein (VLDL), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles could be achieved. Analysis of TGs, phospholipids, total cholesterol, free cholesterol and cholesteryl ester were made in plasma as well as in all lipoprotein fractions.

Total cholesterol was measured by CHOD-PAP (Boehringer Mannheim, Germany), free cholesterol by CHOD-PAP (Wako Chemicals, Germany), TGs by GPO-PAP (Boehringer Mannheim) and phospholipids were analyzed using an enzymatic colorimetric test (Boehringer Mannheim).

Statistical Methods

Statistics were carried out by the statistical software package SPSS for Windows 6.13. p values of <0.05 were considered statistically significant. Laboratory parameters were tested for Gaussian distribution with the KS test (Lillefors) and the Shapiro-Wilks test. Comparison within the group was carried out with the paired t test (Gaussian distribution) and the Wilcoxon test (non-Gaussian distribution).

Results

In all patients the plasma TG values could dramatically be decreased within the 7 days of treatment. Table 2 shows the data of plasma TGs, phospholipids, total cholesterol, free cholesterol and esterified cholesterol, glucose and uric acid at the beginning and end of the study. The mean value of TGs at the beginning of the study was 1,601 mg/dl. The lowest TG value was 402 mg/dl, the highest value was 4,555 mg/dl. After 7 days of treatment with the formula diet TG values could be reduced to a mean of 554 mg/dl with the lowest value at 142 mg/dl and the highest at 2,382 mg/dl. This reduction in plasma TG levels of 61% was statistically significant ($p < 0.018$).

The reduction in plasma cholesterol of 26% from a mean value of 417 to 287 mg/dl was highly significant ($p < 0.0001$). Fasting glucose levels showed a not statistically significant decrease of 8% from a mean value of 167 to 154 mg/dl.

Uric acid levels could be reduced from 6.93 to 6.08 mg/dl (–12%). Although this reduction was not statistically significant, the levels reached a value within the normal range ($\leq$6.5 mg/dl). Phospholipids were reduced from a mean value of 485 to 323 mg/dl. The reduction of plasma cholesterol is mainly due to a decrease in free cholesterol levels (–60%). Plasma esterified cholesterol remained unchanged.

Table 3 shows the concentration of TGs, phospholipids, total cholesterol, free cholesterol and esterified cholesterol in plasma and chylomicrons, VLDL, LDL and HDL. TGs were reduced significantly in all lipoprotein fractions. The TG reduction was greater in chylomicrons (–76%) and VLDL (–60%) than in LDL (–29%) and HDL (–53%). Total cholesterol was reduced in plasma (–31%), in chylomicrons (–77%) and in VLDL (–49%). LDL and HDL fractions showed an increase in total cholesterol (LDL +72%, $p < 0.01$; HDL +21%, n.s.).

Table 3. Statistical data concerning the contents of triglycerides, phospholipids, total cholesterol, free cholesterol and esterified cholesterol in VLDL, LDL, HDL and chylomicrons in patients with severe hypertriglyceridemia receiving the formula diet for a period of 7 days

	Triglycerides mg/dl	Phospholipids mg/dl	Total cholesterol mg/dl	Free cholesterol mg/dl	Esterified cholesterol mg/dl
VLDL					
Day 1					
Mean	708	191	177	110	80
SD	509	119	109	104	46
Min	202	6	58	17	10
Max	2,167	459	459	405	179
Day 7					
Mean	284	102	91	39	56
SD	264	67	65	32	38
Min	42	20	14	5	9
Max	1,079	249	263	125	175
p value	0.02	<0.01	<0.01	<0.01	<0.01
LDL					
Day 1					
Mean	107	64	68	23	49
SD	47	35	46	17	38
Min	27	6	13	5	2
Max	210	138	212	96	140
Day 7					
Mean	76	97	117	30	85
SD	27	43	58	15	43
Min	35	26	21	9	12
Max	145	189	238	72	191
p value	0.05	<0.01	<0.01	<0.01	<0.01
HDL					
Day 1					
Mean	95	89	33	12	20
SD	66	33	13	9	12
Min	24	5	13	0	1
Max	340	175	77	40	48
Day 7					
Mean	45	81	40	9	27
SD	27	32	27	7	12
Min	6	13	13	0	9
Max	129	166	145	39	61
p value	0.01	<0.01	0.526	<0.01	0.093
Chylomicrons					
Day 1					
Mean	691	140	138	93	53
SD	530	105	101	85	42
Min	73	5	28	9	8
Max	1,951	386	419	288	181
Day 7					
Mean	165	43	39	17	23
SD	234	55	50	25	27
Min	12	4	3	1	1
Max	1,099	245	206	91	115
p value	0.02	<0.01	<0.01	<0.01	<0.01

The decrease in total cholesterol in chylomicrons and VLDL was caused by a reduction in free cholesterol and esterified cholesterol, while LDL and HDL showed an increase mainly in esterified cholesterol.

Phospholipids were reduced in plasma (–33%), chylomicrons (–69%), VLDL (–47%), increased in LDL (+52%), and remained stable in HDL.

Discussion

Patients with SHTG are threatened by a number of complications, such as CHD, stroke and pancreatitis. Additionally, hyperglycemia in diabetes mellitus and hyperuricemia are often more severe in patients with elevated TG levels. Therapeutic options include dietary modification, lipid-lowering drugs and even plasma exchange. ω–3 FAs are known to exert positive effects on plasma TG levels [17]. A number of studies showed encouraging results. Singer et al. [18] put patients with type IV and V hyperlipoproteinemia on a mackerel and herring diet for 2 weeks. Thus the patients received a daily amount of 2.2–31 g EPA and 1.0–14.6 g DHA. Serum TG and total cholesterol were significantly reduced.

The effects of a fish oil concentrate containing 85% ω–3 FAs on plasma TG reduction was tested by Mackness et al. [19] over a period of 14 weeks. Plasma TGs could be lowered by 28%.

Herold and Kinsella [20] reviewed the use of ω–3 FAs in human and animal studies. The ω–3 content in the diets was between 8 and 30 g/day. The diets were used over study periods of between 1 week and 3 months. In all studies plasma TG levels as well as cholesterol levels could be significantly reduced.

In most of these studies fish oil was given in addition to a normal diet. For this reason the TG reduction in these studies was not as tremendous as in our study. By giving their patients a low-fat diet combined with fish oil capsules, Phillipson et al. [12] were able to lower TG levels by –79% in patients with type V hyperlipoproteinemia within 4 weeks. It is obvious that not only high doses of ω–3 FAs are necessary to lower TG levels but also a minimal amount of other long-chain FAs in the diet of the patients. This is part of the concept of our formula diet.

In most of the above-mentioned studies as well as in our study a reduction in total cholesterol could also be observed. The discussion on the cholesterol-lowering effect of ω–3 FAs is controversial. No cholesterol reduction in patients with slightly increased plasma cholesterol levels could be observed by Abbey et al. [21]. Their patients received 3.8 g ω–3 FAs over a period of 6 weeks. Plasma TG levels, however, were reduced significantly. The content of total cholesterol did not change. VLDL cholesterol and VLDL TG content were also significantly reduced, whereas LDL cholesterol increased. We found the same results in our study with the formula diet. Abbey et al. [21] did not observe any changes in HDL cholesterol content, whereas in our study a slight increase in HDL could be detected. Additionally Abbey et al. [21] found a decrease in lecithin:cholesterol acyltransferase activity caused by fish oil. The exchange of cholesterol ester and TG between HDL and TG-rich lipoproteins which leads to an increase in cholesterol ester in chylomicrons and VLDL is obviously suppressed by ω–3 FAs from fish oil. This can be seen as a positive anti-atherogenic effect of ω–3 FAs. In our study we were able to observe a reduction in cholesterol ester in chylomicrons and VLDL as well as a slight increase in cholesterol ester content in HDL.

On the basis of these promising results, the concept of the formula diet was developed, containing a high amount of ω–3 FAs and MCT as a main energy source. As is well known in human biochemistry, large amounts of MCT will induce mitochondrial β-oxidation of FA while large amounts of ω–3 FA will induce peroxisomal oxidation of FA. Hence, the cooperation of these two induction mechanisms of FA oxidation is the key concept of the formula diet.

This diet was successfully used as an acute treatment in a number of patients with SHTG and it showed effectiveness in rapidly and safely lowering plasma TG levels in these patients before admitting them to long-term drug therapy. None of the study subject complained about any side effects or adverse events. None of the study subjects quit the study prematurely due to intolerance of the drink.

In conclusion, this formula diet rich in ω–3 FAs and MCT can be used to lower excessively elevated TG levels rapidly, safely and effectively by inducing mitochondrial β-oxidation as well as peroxisomal oxidation of FA.

References

1 Schaefer EJ, McNamara JR, Genest J Jr, Ordovas JM: Clinical significance of hypertriglyceridemia. Semin Thromb Hemost 1988; 14:143–148.

2 Deng LH, Xue P, Xia Q, Yang XN, Wan MH: Effect of admission hypertriglyceridemia on the episodes of severe acute pancreatitis. World J Gastroenterol 2008;14:4558–4561.

3 Albrink MJ, Man EB: Serum triglycerides in coronary artery disease. Arch Intern Med 1959;103:4–8.

4 Dunn FL, Grundy SM, Bilheimer DW, Havel RJ, Raskin P: Impaired catabolism of very low-density lipoprotein-triglycerides in a family with primary hypertriglyceridemia. Metabolism 1985;34:316–324.

5 West KM, Ahuja MM, Bennett PH, et al: The role of circulating glucose and triglyceride concentrations and their interactions with other 'risk factors' as determinations of arterial disease in nine diabetic population samples from the WHO multinational study. Diabetes Care 1983;6:361–369.

6 Fontbonne A, Eschwege E, Cambien F, Richard JL, Ducimetière P, Thibult N, Warnet JM, Claude JR, Rosselin GE: Hypertriglyceridaemia as a risk factor of coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes. Results from the 11-year follow-up of the Paris Prospective Study. Diabetologia 1989;32:300–304.

7 Sarwar N, Danesh J, Eiriksdottir G, Sigurdsson G, Wareham N, Bingham S, Boekholdt SM, Khaw KT, Gudnason V: Triglycerides and the risk of coronary heart disease: 10,158 incident cases among 262,525 participants in 29 Western prospective studies. Circulation 2007;115:450–458.

8 Nordestgaard BG, Benn M, Schnohr P, Tybjaerg-Hansen A: Nonfasting triglycerides and risk of myocardial infarction, ischemic heart disease, and death in men and women. JAMA 2007;298:299–308.

9 Leaf DA, Connor WE, Illingworth R, Bacon SP, Sexton G: The hypolipidemic effects of gemfibrozil in type V hyperlipidemia. A double-blind crossover study. JAMA 1989; 262:3154–3160.

10 Oh RC, Lanier JB: Management of hypertriglyceridemia. Am Fam Physician 2007;75: 1365–1371.

11 Bach AC, Babayan VK: Medium-chain triglycerides: an update. Am J Clin Nutr 1982; 36:950–962.

12 Phillipson BE, Rothrock DW, Connor WE, Harris WS, Illingworth DR: Reduction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia. N Engl J Med 1985;312:1210–1216.

13 Harris WS: N–3 fatty acids and serum lipoproteins: human studies. Am J Clin Nutr 1997;65(suppl):1645S–1654S.

14 Leaf DA: Chylomicronemia and the chylomicronemia syndrome: a practical approach to management. Am J Med 2008;121:10–12.

15 McKenney JM, Sica D: Role of prescription omega–3 fatty acids in the treatment of hypertriglyceridemia. Pharmacotherapy 2007; 27:715–728.

16 Aliget VR, Gandhi M, Braden R, Rezk A, Elam MB: Effect of combination lipid-modifying therapy on the triglyceride lowering effect of fish oil. Am J Med Sci 2007;333:168–172.

17 Bays H: Rationale for prescription omega–3-acid ethyl ester therapy for hypertriglyceridemia: a primer for clinicians. Drugs Today (Barc) 2008;44:205–246.

18 Singer P, Wirth M, Berger I, Voigt S, Gerike U, Gödicke W, Köberle U, Heine H: Influence on serum lipids, lipoproteins and blood pressure of mackerel and herring diet in patients with type IV and V hypertriglyceridemia. Atherosclerosis 1985;56:111–118.

19 Mackness MI, Bhatnagar D, Durrington PN, Prais H, Haynes B, Morgan J, Borthwick L: Effects of a new fish oil concentrate on plasma lipids and lipoproteins in patients with hypertriglyceridemia. Eur J Clin Nutr 1994; 48:859–865.

20 Herold PM, Kinsella JE: Fish oil consumption and decreased risk of cardiovascular disease: a comparison of findings from animal and human feeding trials. Am J Clin Nutr 1986;43:566–598.

21 Abbey M, Clifton P, Kestin M, Beiling B, Nestel P: Effect of fish oil on lipoproteins, lecithin:cholesterol acyltransferase, and lipid transfer protein activity in humans. Arteriosclerosis 1990;10:85–94.