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The triglyceride lowering effect of fish oils is affected by fish consumption

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Abstract

We investigated the efficacy of fish oils in Portuguese patients with hypertriglyceridaemia and mixed hyperlipidaemia, and the influence of fish consumption on the triglyceride lowering capacity of fish oils. Forty patients participated in this double-blind study, consisting of a 4-week dietary or wash-out baseline period after which patients were randomly assigned to receive either 12 fish oil capsules (3.6 g/day of omega 3) or similar 12 soya oil capsules per day for a period of 2 months. There were no statistically significant changes of total, HDL or LDL-cholesterol, and triglycerides. Nevertheless, triglycerides increased 19.9% with soya oil and decreased 27.8% with fish oils. Also, there was an inverse relationship ($\rho = -0.352$) between fish consumption and fish oils effect on triglycerides, and the triglyceride lowering with fish oils increased (from 27.8% to 44.4%), reaching borderline significance, if we excluded patients consuming one or more meals with fish per day. Glucose increased 11% ($P = 0.0047$) with fish oils. These findings suggest that the triglyceride lowering effect of fish oils is affected by fish consumption, and confirm that fish oils increase blood glucose levels in diabetics and non-diabetics.

Keywords: Fish oils; Triglycerides; Fish consumption; Diabetes

1. Introduction

Evidence in favour of beneficial effects of dietary fish oil on prevention or retardation of atherosclerosis, thought to be related to the high quantities of omega-3 polyunsaturated fatty acids found in many types of fish, has been obtained from epidemiological studies in man and from experimental studies in animals [1]. These fatty acids have been reported to have anti-inflammatory and immunosuppressive effects, reduce platelet aggregation and monocyte adhesion, increase erythrocyte deformability, improve fibrinolysis, alter prostaglandin synthesis, stimulate endothelium-derived relaxing factor synthesis, lower blood pressure, plasma triacylglycerol and very low density lipoprotein, and even to protect against peroxidation [2].

In Portugal, contrasting with other industrialized western countries, mortality from stroke has a higher incidence than that from coronary heart disease

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(respectively 194/100 000 and 79/100 000 in 1990). This discrepancy may be due to the protection conferred against coronary heart disease by the favorable Mediterranean diet, Portuguese usually are high consumers of fish, olive oil, red wine and vegetables, with the high mortality from stroke being a consequence of a salt intake above 15 g per person per day [3]. Unfortunately, the Portuguese diet is being progressively westernized. Bearing in mind the characteristics of the Portuguese, we thought that it would be interesting to study the effect of supplying fish oils to Portuguese hypertriglyceridaemic and mixed hyperlipidaemic patients, and to investigate whether fish consumption affected the triglyceride lowering capacity of fish oils or not.

2. Materials and methods

Eligible patients were 18 to 70 years old with hypertriglyceridaemia (triglycerides >200 mg/dl) or mixed hyperlipidaemia (total cholesterol >200 mg/dl and triglycerides >200 mg/dl). All those with hypersensitivity to the drug, serum creatinine >1.5 mg/dl, liver disease, non-atherosclerotic neurologic diseases, insulin-dependent diabetes mellitus, myocardial infarction or stroke in the previous 6 months, heart failure, premenopause, secondary hypercholesterolaemia or more than 96 g of alcohol consumption per day were excluded. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki, was approved by the Ethics Committee of the hospital, and all patients gave informed written consent.

This was a double-blind study with 2-month therapy. After at least 1 month of diet or washout period, all participants were randomly assigned to receive either 12 capsules/day (4 caps tid) of fish oil (12 g/day, 3.6 g/day of ω-3, 60% EPA and 40% DHA), supplied by Hebron, Caruaru, Brazil, or of soya oil (12 g/day), prepared in a Portuguese laboratory. Compliance was assessed by pill count.

A sequential sample of 40 patients coming to the Atherosclerosis Out-Patient Clinic of the University Hospital of Coimbra was studied. Analysis and clinical examinations were performed at weeks (−4), (0), (+4) and (+8). At the initial clinical examination, besides the search for exclusion criteria, body mass index, blood pressure, and fish (average number of meals with fish per week), tobacco and alcohol consumption were registered. Patients with systolic ≥160 and/or diastolic BP ≥95 mmHg or taking antihypertensive drugs were considered as hypertensives.

Total, HDL and LDL cholesterol, triglycerides and apoproteins A-I and B100 were analyzed (all values in mg/dl). Serum total cholesterol and triglycerides were determined by enzymatic methods on an automated analyzer (Hitachi 737). HDL-C and LDL-C were determined on an automated analyzer (Hitachi 705), the first with a Human GBD mbH kit, after precipitating other lipoproteins with phosphotungstic acid and magnesium chloride, and the second after specific precipitation with a bioMérieux kit. Apoproteins A-I and B100 were quantified by rate nephelometry (Beckman immunochemistry systems).

Laboratory safety tests consisted of hematology and blood chemistries (glucose (mg/dl), creatinine (mg/dl), creatine kinase (CK) (U/l), alanine (ALT) and aspartate (AST) aminotransferase (U/l), and alkaline phosphatase (U/l).

Data were evaluated using StatView 512+™ from BrainPower Inc. The results are presented as mean±standard error of the mean. Statistical significance was assessed with paired *t*-test (2-tail), and with 2-factor ANOVA for repeated measures. Owing to being not normally distributed, triglycerides were log transformed before statistical analysis. Correlations were calculated with Spearman Rank Correlation Coefficient on untransformed data.

3. Results

The data presented here are related only to 35 patients (25 females and 10 males), since 5 (4 males and 1 female, 2 during the first 4 weeks and 3 between the 5th and the 8th week, all with soya oil) abandoned the study because of adverse effects that they attributed to the drug (one with acute pancreatitis and the others with eructations, nausea, sensation of repletion, meteorism and epigastralgias). We did not rechallenge these patients with soya oil capsules or with the gel of the capsules only, so we cannot attribute definitely these side effects to soya oil. Minor and transitory side effects were referred

Table 1
Comparison between baseline characteristics of patients completing the study

	Fish oil	Soya oil
Patients (no.)	20	15*
Sex		
Male	17 (85)	8 (53)
Female	3 (15)	7 (47)
Age	50.6±2.8	56.1±2.7
BMI	28.9±0.8	30.6±0.9
BP (mmHg)		
Systolic	150.7±6.4	158.3±6.6
Diastolic	87.6±3.2	92.3±2.4
Heart rate	67.3±1.6	66.1±2.2
Fish consumption		
No. meals/week	5.0±0.5	4.7±0.6
Wine drinkers	12 (60)	4 (27)
Alcohol (g/day)	46.4±7.5	37.2±6.3
Smokers	2 (10)	0 (0)
Hypertension	10 (50)	11 (85)
NIDDiabetes mellitus	4 (20)	2 (13)

Results presented as mean±standard error of the mean or No. (%).
*The data presented here is related only to 15 patients, since 5 abandoned the study.

by 6 patients taking fish oils and 1 taking soya oil. Ages of patients completing the study ranged from 30–70 years. Soya oil patients consumed a mean of 11.4 and fish oils patients 11.5 caps/day. The two groups were reasonably matched at baseline (Table 1).

Table 2 shows the values of the studied parameters at baseline and after 8 weeks of therapy with soya oil and fish oil. We had to log transform triglycerides before statistical analysis because they are not normally distributed, having a skewness of 2.16 in soya oil patients and of 3.53 in fish oil patients at baseline. The different effect of soya oil and fish oils on TG and LDL-C is of borderline significance (respectively $P=0.0867$ and $P=0.0872$ between groups, 2-factor repeated measures Anova).

Sex, body mass index, hypertension, diabetes and alcohol consumption did not affect the fish oils effect on lipid parameters (2-factor repeated measures ANOVA, and simple regression).

Table 3 shows the change of laboratory safety tests with both oils. There is a significant increase in glucose levels both in diabetics and non-diabetics.

In order to study the influence of fish consumption on the triglyceride lowering effect of fish oils we divided the sample into tertiles according to the number of meals with fish consumed per week. Table 4 shows these results, clearly demonstrating that fish oils have no effect on the triglyceride levels of patients consuming fish more than 6 times per week. The same evidence is shown in Fig. 1. There is an inverse correlation between the number of meals with fish per week and the triglyceride lowering effect of fish oils (ρ corrected for ties$=-0.352$, $P=0.0735$, $n=19$). This correlation was calculated for only 19 patients because data of fish consumption of one patient was lacking.

4. Discussion

With the present study we aimed at examining both the effect of short term supplementation with ω-3 fatty acids on the lipid profile of Portuguese patients (usually are high consumers of fish, olive oil, red wine and vegetables) with hyper-

Table 2
Effect of soya oil and fish oils on serum lipids and apoproteins

	Soya oil ($n=15$)				Fish oil ($n=20$)			
	Baseline	Week 8	%	P	Baseline	Week 8	%	P
Total cholesterol	291±15	305±16	—	—	253±15	249±12	—	—
Triglycerides*	391±46	469±64	↗19.9	—	431±114	311±55	↘27.8	—
HDL-cholesterol	37.4±3.1	37.1±3.4	—	—	33.6±2.2	33.5±1.5	—	—
LDL-cholesterol**	151±17	137±14	↘10.0	—	117±11	126±9	↗7.7	—
apoA-I	184±8.9	151±9.2	↘17.9	0.0001	159±8.0	131±6.5	↘17.6	0.0001
apoB100	222±11	217±14	—	—	188±10	185±9.4	—	—

*$P=0.0867$ between groups (2-factor repeated measures Anova).
**$P=0.0872$ between groups (2-factor repeated measures Anova).

Table 3
Effect of soya oil and fish oils on biochemical parameters

	Soya oil				Fish oil			
	Baseline	Week 8	%	P	Baseline	Week 8	%	P
Glucose	100±4.8	104±6.6	—	—	109±11.7	121±14.5	↗11.0	0.0047
Glucose — non-insulin-dependent diabetes mellitus (n=4)					181±38.9	217±42.5	↗19.9	0.0351
Glucose — non-diabetics (n=15)					89.5±3.0	95.9±4.1	↗7.2	0.0218
Uric acid	4.97±0.53	5.53±0.44	↘11.3	—	5.41±0.33	5.32±0.33	—	—
ALT	34.2±6.0	38.4±8.8	↘12.3	—	27.5±4.8	29.3±3.3	—	—
AST	25.6±3.3	22.9±2.4	—	—	22.5±2.7	24.0±2.1	—	—
Alkaline phosphatase	78.8±3.4	85.4±5.0	—	—	68.5±5.2	66.5±6.1	—	—
Creatinine	0.92±0.03	0.95±0.04	—	—	1.00±0.04	1.02±0.04	—	—
Creatine kinase	94±10.5	87±10.7	—	—	121±12.4	135±16.7	↗11.6	—

Evolution of the studied safety parameters with soya oil and fish oils. As glucose increased in the fish oils group, diabetic (all type 2) and non-diabetic patients were computed separately.

Table 4
Influence of fish consumption on the triglyceride lowering efficacy of fish oils

Fish consumption (No. meals/week)	n	Triglycerides			
		Baseline	Week 8	%	P
1st tertile (1–4)	7	344±61	222±22	↘35.5	0.0132
2nd tertile (5–6)	6	660±356	335±134	↘49.2	—
3rd tertile (7–9)	6	325±52	388±112	↗19.4	—
1st+2nd tertiles	13	502±179	279±67	↘44.4	0.0622

Triglyceride lowering effect of fish oils in subgroups of patients, divided into tertiles according to the number of meals with fish consumed per week.

triglyceridaemia and mixed hyperlipidaemia, and the influence of fish consumption on the triglyceride lowering capacity of fish oils. This was a double-blind study in which patients were randomly assigned to receive either fish oil (3.6 g/day of ω-3) or soya oil for a period of 2 months. The soya oil group was considered as a control group, notwithstanding the fact that it is rich in ω-6 unsaturated fatty acids and has some α-linolenic acid, and it may have its own effects [4–7], although not pronounced.

Contrasting results of fish oils on circulating lipids have been reported by various authors, particularly concerning the effect of fish oil on total cholesterol, LDL-C and HDL-C [8]. These discrepancies may be

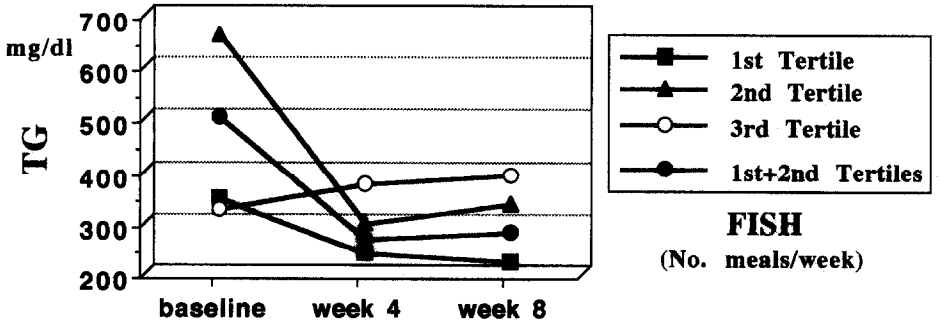

Fig. 1. The triglyceride (TG) lowering effect of fish oils in subgroups of patients, divided into tertiles according to the number of meals with fish consumed per week.

explained by a small effect of this compound on these parameters, by insufficient sample size, by the variability of doses and formulations of ω-3 fatty acids administered [8], and by the dietary fat intake [9].

Unexpectedly, and without decreasing HDL_2 (data not shown) and HDL-C, both soya oil and fish oils decreased apoA-I (Table 2), although we cannot exclude an interassay variation. ApoB100 did not change either with soya oil or with fish oils. Others did not find any significant influence of fish oils on serum apoA-I or apoB100 levels [2,10–14], nor any effect of soya oil on apoA-I levels [5,6], the HDL-C reducing effect of polyunsaturated fatty acids being well-known, though. Shepherd et al. [15] reported a 26% decrease in apoA-I synthesis in subjects consuming a diet that provided 40% of calories from fat with a P/S ratio of 4.0.

The predominant effect of long chain ω-3 fatty acids on lipid and lipoprotein metabolism in cell culture systems, animals or humans is to reduce triglyceride concentrations [8,16], by decreasing the activity of acyl-CoA:1,2-diacylglycerol acyl transferase, the last enzyme in triglyceride synthesis [16]. The average reduction of triglycerides is dose related [9,17], the minimal effective dose of ω-3 fatty acids being about 1 g daily and a plateau being reached at between 5 and 10 g [17].

By showing a reduction in triglyceride levels with no change in total and HDL-C, and a slight increase in LDL-C and glucose, as we have already shown [18], our results are in agreement with many of the studies so far published [8,16,19–21]. This latter effect may limit the use of fish oils in diabetic patients, although the question as to whether fish oils should be given to type II diabetics has not been settled, the results of several studies being contradictory [10,11,19–26].

The lack of a statistically significant change on triglycerides with fish oils could be partially due to the fact that the Portuguese diet is rich in fibre [3], which may interfere with fat digestibility and absorption [27], affecting fish oils absorption. Moreover, epidemiological data suggest that cardiovascular protection is obtained with a fish consumption as low as one or two meals per week [28], and that maximum benefits on lipid profile of the general population are obtained with three or four meals per week [29]. As our patients are high fish consumers, this may have decreased the lowering effect of fish oils.

Interestingly, our results show that moderate doses of fish oils can further improve the lipid profile of the average fish consumers, but high consumers of fish derived no benefit on their triglycerides from the administered dose of fish oils. Accordingly, in our patients there was an inverse relationship between fish consumption and fish oils effect ($\rho = -0.352$, $P = 0.0735$, $n = 19$), and the percentage of triglyceride lowering with fish oils increased (from 27.8% to 44.4%), reaching borderline significance, if we excluded patients consuming one or more meals with fish per day (Table 4). The group of patients consuming one to four fish meals per week significantly lowered triglyceride levels with fish oils owing to a not too high standard error of the mean. The highest fish consumers suffered a moderate, although not statistically significant, increase in triglyceride levels, precisely the same percentage seen with soya oil, perhaps a consequence of an extra charge of the diet with fatty acids. These data clearly demonstrate that fish consumption is an important modulator of fish oil efficacy.

Acknowledgments

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