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Omega-3 Fatty Acids Reduce Hyperlipidaemia, Hyperinsulinaemia and Hypertension in Cardiovascular Patients

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Cardiovascular disease (CVD) is associated with hyperlipidaemia, hypertension and frequently with insulin resistance, which in general are not alleviated by antilipidaemic drugs. Our objective was to examine whether a supplemented diet containing eicosapentaenoic (EPA) and docosahexaenoic (DHA) omega-3 fatty acids (n-3 FAs), in addition to lecithin, extracts of rosemary and curcumin (n-3 FAs + supplements), can reduce the levels of serum lipids, insulin and hypertension in documented CVD patients (pts) treated by statins and/or bezafibrates.

In a double-blind placebo-controlled trial of parallel design, 78 pts, age 69.7 ± 4.1 years treated by antilipidaemic drugs, were randomly assigned to receive daily 7 g of the n-3 FAs + supplements in a form of a bread spread (Yamega Ltd, Israel) or analogous spread made of olive oil as placebo. The participants were recommended to reduce the consumption of omega-6 fatty acids for 12 weeks. The average values ± SD before and after dietary supplementation were compared.

62 pts (34 in the n-3 FAs + supplements group and 28 in the control group) completed the study. In the n-3 FAs + supplements group we observed a significant decrease ($p < 0.05$) of total serum cholesterol (17.2 %), LDL-cholesterol (16.2 %), triglycerides (39.6 %), and insulin (35.2 %) in the hyperinsulinaemic subjects (> 20 microunits/ml). Hypertension (> 140/90 mmHg) which was positively correlated to hyperinsulinaemia, decreased significantly especially in the systolic blood pressure. No significant changes in HDL-cholesterol and glucose were observed. In the placebo group we observed a significant decrease ($p < 0.05$) in the LDL-cholesterol values of 10.6 % but no significant changes in the other parameters. No side effects were reported during the study in any of the participants. Our findings demonstrate that the incorporation of the dietary supplement containing EPA and DHA omega-3 FAs supplemented with lecithin, rosemary and curcumin can reduce significantly the risk factors for CVD. *J Clin Basic Cardiol 2002; 5: 229–31.*

Key words: hypertension, hyperlipidaemia, hyperinsulinaemia, cardiovascular disease, omega-3 fatty acids

The human race evolved consuming a diet that contained about equal amounts of n-3 and n-6 essential fatty acids. Over the past century there has been an enormous increase in the consumption of n-6 fatty acids due to the increased intake of vegetable oils in particular from corn, sunflower, safflower, cottonseed and soybeans. Today, the ratio of n-6 to n-3 fatty acids in the Western diet, including ranges from approximately 10:1 to 20:1 in comparison to the traditional range of 1–2:1 [1, 2]. The high intake of n-6 fatty acids affects a variety of pathophysiological processes, ranging from immune-inflammatory reactions to atherogenesis and tumorigenesis [3], increased susceptibility of LDL to oxidation [4, 5], enhanced prothrombotic and proaggregatory processes which lead to high blood viscosity, vasospasm, vasoconstriction and decreased bleeding time [6], reduced level of HDL-cholesterol [7, 8] which together lead to an increased risk for coronary thrombosis, coronary heart disease, acute myocardial infarction and mortality [7].

Furthermore, a high intake of linoleic n-6 FA increases the secretion of insulin, and/or reduces insulin catabolism [9, 10], causing impaired insulin actions [11, 12], and leading to insulin resistance syndromes [13, 14], termed syndrome X [13]. On the other hand, epidemiological, clinical and experimental studies have shown an inverse correlation between consumption of fish or other sources of dietary n-3 fatty acids and cardiovascular impairments [15], risk of ischaemic heart disease [16] and incidence of sudden cardiac death [17, 18]. In addition, a series of studies attributed to n-3 FA attenuation in the development of atherosclerosis or restenosis [19], stabilization of arrhythmia [17, 18] changes in the LDL-cholesterol composition with less atherogenic LDL particles and reduction of apolipoprotein B [20, 21], lipoprotein (a) [22], fasting and postprandial plasma triacylglycerol [20, 23] and hypertension [24, 25]. No less important is that n-3 FAs were found to reduce hyperinsulinaemia [26] and insulin resistance [10]. Numerous reports attributed to extracts of curcumin and rosemary therapeutic antioxidant activities, prevention of spasmogenic disorders, inflammatory diseases, atherosclerosis and ischaemic heart diseases [27–30]. In the present study it was demonstrated that a diet containing n-3 fatty acids supplemented with lecithin, curcumin and rosemary extracts, improves dyslipidaemia, hypertension and hyperinsulinaemia in CVD pts and may therefore be used as an effective adjuvant to antilipidaemic drugs.

Materials and Methods

Patients and Randomization

In a double-blind placebo-controlled trial of parallel design, 78 documented CVD pts (by coronary angiogram or at least by 201-Thallium heart scan), age 69.7 ± 4.1 y, were enrolled. The clinical characteristics of the pts were as follows: 4 pts with post myocardial infarction (MI) with stable anginal syndrome (AP), 11 pts with post MI and no AP, 25 pts with stable AP, 38 pts without symptoms, 7 of them were post percutaneous transluminal coronary angioplasty and 5 pts were post coronary artery bypass grafting, and 4 pts with congestive heart failure. None of the pts were obese or alcohol abusers. They were followed by the Mishmar Hayarden Cardiac and Rehabilitation Institute-Givataym, and randomly assigned to

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receive 7 g/d of a dietary concentrated supplement (n-3 FAs+supplements group; composition given below) or placebo, and recommended to reduce the consumption of omega-6 fatty acids for 12 weeks. The eligibility criteria were existence of CVD and dyslipidaemia treated by statins and/or bezafibrates for at least 3 months before entering the study without satisfactory results, so that an increase of medication doses had been considered. The antilipidaemic drug treatment was continued during the study.

Dietary Supplement Composition
67 % n-3 FA (Pronova Biocare, Norway, 185 mg EPA and 465 mg/g DHA), 14 mg/g lecithin, and extracts of rosemary (Rosemarinus officinalis Linn.) and Curcumina longa L. (Dr. Marcus, GmbH) 4.4 mg and 3.0 mg/g respectively, in the form of a bread spread (Yamega Ltd., Israel). Bread spread of only olive oil (Yamega Ltd., Israel) was used as a placebo.

Compliance
The patients were recommended to reduce the consumption of omega-6 fatty acids, and were asked to visit the Institute every 2 weeks in order to receive the dietary supplement spreads and to inform the personnel on their compliance.

Blood Pressure
Blood pressure was measured before and every two weeks, by stethoscope, after 15 min rest in a horizontal position.

Blood Analyses
Fasting venous blood was collected before and at the end of the study. The laboratory test included total, LDL, HDL-cholesterol, triglycerides, glucose and insulin. Biochemical tests were performed automatically in a Hitachi 747 device at 37 °C (reagents from Boehringer, Mannheim, Germany). Insulin was assayed automatically in an Immulite device by chemoluminescence method (Diagnostic Product Corporation, Los Angeles, USA).

Statistical Analysis
The Mann-Whitney test was used. The significance of the difference between groups was analyzed by repeated measures of variance (ANOVA) using the computer program Statistics 5.0. Results are expressed as mean ± SD in addition to p-values.

Results

62 pts, 34 in the omega-3 FAs + supplements group and 28 in the placebo group, completed the study. Table 1 summarizes the blood test results before and at the end of the study in both groups. The results in the omega-3 FAs + supplements group indicated a significant decrease ($p < 0.05$) of total cholesterol (17.2 %), LDL-cholesterol (16.2 %), triglycerides (39.6 %) and insulin (35.2 %) in the hyperinsulinaemic pts, (18 out of 34), and no significant changes in the HDL-cholesterol and glucose values. 9 out of the 18 hyperinsulinaemic pts showed high values of systolic blood pressure (175±12 mmHg) which decreased at the end of the study to 130.8 ± 3 mmHg while diastolic values decreased from 95 ± 3 to 82.5 ± 3 mmHg.

In the placebo group a significant decrease in the LDL-cholesterol of 10.6 % was observed with no changes in the other parameters. No side effects were reported in any of the participants of both groups.

Discussion

Lipid lowering drugs like the statins lower LDL-cholesterol levels, increase HDL-cholesterol, and reduce triglycerides [31]. However, the CVD pts in our study, despite being treated by these antilipidaemic drugs, presented before the study high blood cholesterol, LDL-cholesterol and very high values of triglycerides (see Tab. 1). In addition, 34 out of 62 pts, presented also high insulin levels (> 20 mU/ml) and 16 of them were under hypertension.

The best evidence for the influences of dietary fats on human health is provided by the Japanese people. During the past 40 years, the average intake of total fats in Japan has increased to approx. 60 g/day, still considerably below the levels in Western countries.

The average intake of n-6 and n-3 FA in Japan has also increased from 4 g/d and 2g/d to 12g/d and 3g/d respectively, so that the ratio between n-6 and n-3 FA increased from 2 to 4 while in the Western countries the ratio is 10–20:1 [1]. According to Okuyama et al. [32] this increase in n-6 FA and relative n-3 deficiency are major risk factors for cancers, cardiovascular and cerebrovascular diseases and also for allergic hyperreactivity.

Hypertriglyceridaemia and hypertension are the most common abnormalities associated with hyperinsulinaemia and insulin resistance [13, 14] and strong predictors of risk for coronary heart disease (CHD) and myocardial infarction. Elevated plasma triacylglycerol concentrations are associated with other CHD risk factors, namely reduced HDL-cholesterol and a preponderance of highly atherogenic, LDL-cholesterol. Other pathological responses, such as impaired coagulation and pancreatitis, have also been attributed to hypertriglyceridaemia [33].

Several factors may lead to hyperinsulinaemia and insulin resistance, among them high consumption of linoleic n-6 FA. On the

Table 1. Average values ± SD of serum cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose insulin# and blood pressure* before and after 12 weeks under diet supplements; number of participants: omega-3 FAs + supplements group (n-3 + suppl) = 34, placebo group (placebo) = 28

	n-3 + suppl	Placebo	n-3 + suppl	Placebo	n-3 + suppl	Placebo
	Cholesterol [mg/dl]		LDL-Cholesterol [mg/dl]		HDL-cholesterol [mg/dl]	
Before	256.2 ± 37.5	250.4 ± 34.6	185.0 ± 36.1	183.6 ± 37.2	42.4 ± 22.3	43.8 ± 21.6
After	212.1 ± 29.6**	241.2 ± 36.2	150.2 ± 21.4**	164.2 ± 35.4**	46.8 ± 18.4	42.8 ± 20.4
	Triglycerides [mg/dl]		Glucose [mg/dl]		Insulin [mU/ml]#	
Before	246.8 ± 41.0	241.4 ± 38.6	108.4 ± 24.6	100.8 ± 22.2	29.6 ± 5.8	28.8 ± 6.1
After	148.9 ± 25.2**	239.5 ± 36.9	102.2 ± 18.4	103.8 ± 28.1	18.4 ± 3.1**	27.8 ± 7.2
	Systolic Blood Pressure [mmHg]		Diastolic Blood Pressure [mmHg]			
Before	175.5 ± 12	170.0 ± 15	95.0 ± 3	95.5 ± 5		
After	130.0 ± 8**	165.5 ± 10	82.5 ± 2**	90.0 ± 5		

Insulin values only from hyperinsulinaemic subjects (> 20 mU/ml); 18 in the n-3 + suppl group and 16 in the placebo group; * Blood pressure only from hypertensive pts, all of them hyperinsulinaemic; 9 in the n-3 + suppl group and 7 in the placebo group; ** Significantly different from starting values; P < 0.05

other hand, n-3 FA prevent hyperinsulinaemia [26] and insulin resistance [10]. In addition, recent studies attributed to curcumin and rosemary extracts antioxidant activities in addition to prevention of spasmotic disorders, inflammatory diseases, atherosclerosis, and ischaemic heart diseases [27–30].

In line with this evidence we may attribute the beneficial changes observed in the blood profile (Tab. 1) of the n-3 FAs + suppl pts group, to n-3 FA and the other active ingredients in the dietary spread. The results of this study reinforce many other studies showing that n-3 FA, especially when combined with curcumin and rosemary extracts, may alleviate and/or prevent CHD and other related diseases [16–23]. In addition, the results of this study indicate that the combination of simvastatin and fish oil has better therapeutic effects than simvastatin alone [31], which deserve further investigation.

Another aspect to be considered is the statins' pharmacological and clinical effects. In general, the safety and tolerability profiles for all statins currently in use is of less than 2 % incidence of undesirable effects. The most common adverse effects of simvastatin are gastro-intestinal disturbance, myositis and myopathy. However, rhabdomyolysis leading to renal failure [34] and thyroid follicular adenoma [35] were also reported. Intake of n-3 fatty acid may therefore permit the reduction statins doses, and thus alleviate the adverse effects.

Conclusion

Many studies have shown that diets may interfere with a series of risk factors of CVD not modulated by antilipidaemic drugs. Our study confirms and reinforces studies showing that n-3 FAs combined with lecithin, curcumin and rosemary extracts have an important beneficial influence on dyslipidaemia, hypertension and hyperinsulinaemia.

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