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STUDIES ON VERY LONG CHAIN MARINE N-3 FATTY ACIDS IN PATIENTS WITH ATHEROSCLEROTIC HEART DISEASE WITH SPECIAL FOCUS ON MECHANISMS, DOSAGE AND FORMULAS OF SUPPLEMENTATION

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Abstract – Based on experience from randomised trials with n-3 PUFA we intend to answer some relevant questions in patients with coronary heart disease. In the SHOT study supplementation with 3.4g/day of highly concentrated n-3 PUFA for 1 year significantly reduced the occlusion rate of venous aortocoronary bypass grafts, and this effect correlated significantly to the change in serum levels of n-3 fatty acids. In the CART study 5.1g/day of highly concentrated n-3 PUFA did not reduce the incidence of restenosis after 6 months. If anything, a negative effect was observed. The background for this was probably a prooxidative and proinflammatory mechanism as elucidated in substudies. In the OVITES trial the addition of vitamin E did not counteract the proinflammatory effect of high amounts of n-3 PUFA supplementation as observed in CART, although circulating oxidative substances were unaffected. In the "Fiord-to-table" study replacement of fish oils by vegetable oils in the feed of farmed Atlantic salmon was mirrored in the fatty acid profile of the salmon fillets as well as in that of serum from patients after ingesting about 700g/week for six weeks. A parallel reduction of the proinflammatory profile was observed only in patients who ingested salmon fed on fish oil.

Key words: n-3 PUFA, PTCA, CABG, peroxidation, inflammation, farmed fish.

INTRODUCTION

Focus on the possible beneficial effects of the very long-chain marine n-3 fatty acids (PUFA) in atherothrombotic heart disease was first brought about by the studies of Bang and Dyerberg on Greenland Eskimoes in the 1970ies.

Abbreviations: AA, arachidonic acid;**CABG,** coronary artery by-pass grafting; **CART,** coronary angioplasty restenosis trial; **CHD,** coronary heart disease; **CRP,** c-reactive protein; **DHA,** docosahexaenoic acid; **EPA,** eicosapentaenoic acid ; **IL-6,** interleukin-6 ; **LPS,** lipopolysaccharide; **NFkB,** nuclear transcription faktor κB; **NYHA,** New York Heart Association; **OVITES,** Omega-3 Fatty Acids and Vitamin E Study; **PCI,** percutaneous coronary intervention; **PDGF,** platelet-derived growth factor; **PPAR,** peroxysome proliferator activated receptor; **PTCA,** percutaneous transluminal coronary angioplasty; **PUFA,** very long-chain marine n-3 fatty acids; **SHOT,** SHunt Occlusion Trial; **TBARS,** thio-barbituric-acid-reactive substances; **TM ,** thrombomodulin; **TNFα,** tumor necrosis factor alpha; **tPAag,** tissue plasminogen activator antigen; **vWF,** von Willebrand Factor; **VCAM-1,** vascular cell adhesion molecule-1.

They suggested that the very high intake of n-3 PUFA by the Eskimoes was responsible for the low prevalence of coronary heart disease (CHD) as compared with the regular Danish population. In addition, the bleeding tendency among the Eskimoes was taken as a sign of n-3 PUFA influence on their platelet function. (2,5,6,7).

Later on, large epidemiological studies have convincingly showed that regular intake of fish reduce the proneness to atherothrombotic disease states, and that a certain dose-response-effect might be present (20). This has again been associated with the intake of PUFA, and recommendations of at least 1 g/day of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have been given (21).

A series of possible mechanisms for the positive effects of PUFA in atherothrombosis have been proposed and also elucidated in animal models, cell cultures and ex vivo experiments.
The exchange of n-6 fatty acids like arachidonic acid (AA) with EPA and DHA have been shown

to influence platelet reactivity, endothelial function and inflammatory processes in an antiatherothrombotic manner (19).

Based on an increasing literature on the beneficial effects of PUFA in atherothrombosis, the main pathogenetic process in cardiovascular morbidity and mortality in Western populations, commercially available purified concentrates of fish oil in capsules have been presented.

An inherent possible negative effect has also been focused related to the proneness to peroxidation of these highly unsaturated fatty acids, possibly more pronounced in highly concentrated commercial products than in the naturally occuring sea food (25).

AIMS OF THE REVIEW

In the early 1990ies when we started our research on PUFA, only few larger randomised clinical trials on the effect of PUFA in atherosclerotic disease states in humans were reported.

We hereby take the opportunity to review our experience related to the following dominating aims:

1. Does supplementation with concentrates of PUFA positively influence the occlusion rate of aorto-coronary bypass grafts?
2. Does supplementation with relatively high amounts of concentrates of PUFA counteract the restenosis process occurring after percutaneous transluminal coronary angioplasty?
3. Is the proinflammatory effect of high doses of PUFA concentrates observed in 2. counteracted by additive supplementation with the antioxidative vitamin E?
4. Has the increasing replacement by vegetable oils for fish oils in the feeding of farmed salmon any measurable effects in humans with atherosclerotic coronary heart disease?

These questions are related to the conduction of randomised trials, which will be discussed separately, before a common conclusive commentary.

DOES SUPPLEMENTATION WITH CONCENTRATES OF PUFA POSITIVELY INFLUENCE THE OCCLUSION RATE OF AORTO-CORONARY BYPASS GRAFTS?

Background

In the early 1990ies coronary artery bypass grafting (CABG) was an established treatment option for symptomatic coronary artery disease, and it was estimated that 368 000 CABG procedures were performed in the US in 1989. In Norway approximately 3 200 patients underwent CABG in 1992. A great challenge in the follow-up situation after CABG was the experience of 15-40% of occlusion of vein grafts during the first postoperative year.

The mechanism of occlusion was thought to be mainly atherothrombotic. Thus, the thoracic surgeons “constructed” a model for studying the possible effect of PUFA on atherothrombotic occlusion of such vein grafts.

Design of study

On this background the SHunt Occlusion Trial (SHOT) (8) was designed. After power calculations based on an estimated 40% reduction of an assumed occlusion rate of 20% in vein grafts after 1 year, 610 patients were included to be randomised to 3.4g/day of highly concentrated EPA+DHA (Omacor®, Pronova, Norway) or control on top of either aspirin or warfarin as specific antithrombotic treatment. The primary end point was 1 year graft patency, and 95% of the patients were assessed with coronary angiography after 1 year. The serum fatty acid profile was examined at baseline and at study end to objectively assess compliance and to study potential relation to the end point.

Results

Totally, 14 patients died during the observation period, equally distributed among the randomised groups. Altogether vein graft occlusion rates per distal anastomosis were 27% in the PUFA group and 33% in the control group (OR 0.77, 95%CI 0.60-0.99, p=0.034). In the PUFA group 43% of the patients had ≥1occluded vein graft compared with 51% in the control group (OR 0.72, 95%CI0.51-1.01, p=0.05). Moreover, in the entire patient group there was a significant trend to fewer patients with vein graft occlusion with increasing relative change in serum n-3 fatty acids during the study period (p for trend=0.004). As a fact in the highest quartile of relative changes in serum n-3 fatty acids the vein graft occlusion rate was only half of that in the lowest quartile (Figure 1).

Conclusion

We concluded that supplementation with n-3 fatty acids in patients undergoing coronary artery bypass grafting significantly reduced the incidence of vein graft occlusion, and that an

inverse relation was observed between the relative change in serum n-3 fatty acids and vein graft occlusion after 1 year.

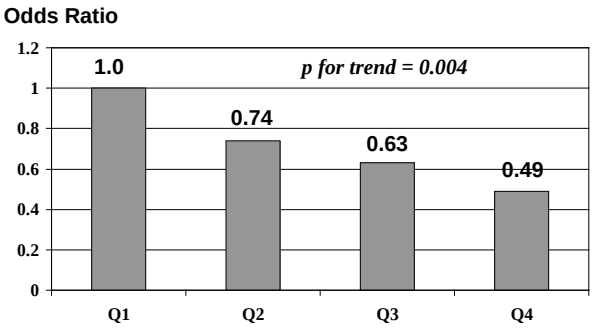

Figure 1. Patients with vein grafts occlusions in quartiles of the relative change in serum n-3 fatty acids (from the SHOT-study). Data from 524 patients with vein shunts. p-value refers to trend analysis.

DOES SUPPLEMENTATION WITH RELATIVELY HIGH AMOUNTS OF CONCENTRATES OF PUFA COUNTERACT THE RESTENOSIS PROCESS OCCURRING AFTER PERCUTANEOUS TRANSLUMINAL CORONARY ANGIOPLASTY?

Background

Since the first report on percutaneous transluminal coronary angioplasty (PTCA) for coronary artery stenosis by Gruentzig in 1978 (11) this method with modifications has emerged as the "first method of choice" in isolated stenoses of the coronary arteries. Initially, this was applied in patients with angina pectoris and with principally symptomatic effect. In later years the procedure has been brought into routine also for patients with occluded arteries in acute situations with ST-elevation myocardial infarctions.

The greatest methodologial challenge has from the beginning been the high rate of restenosis, initially with the "balloon only" in up to 50% of the patients within the first 3-6 months. Later, with the introduction of stenting with the use of steadily improved stents, the restenosis rate has decreased to about 10-15%.

The mechanism of restenosis is discussed to be dominated by phenotypically changed smooth muscle cells from the media proliferating into the heavily wounded intima with production of matrix proteins. This process has been thought to be mediated by growth factors, and focus has been on platelet-derived growth factor (PDGF) among others (26). The expression of this growth factor, being produced by platelets as well as by other cell types in the atherosclerotic plaque, was reported to be inhibited by n-3 fatty acids in cell cultures (10).

Design of study

On this background, and before the introduction of stents, which contributed to change the acronym of the procedure from PTCA to PCI (percutaneous coronary intervention), the Coronary Artery Restenosis Trial (CART) (13) was launched. At that time some smaller studies also indicated a possible dose-response effect of PUFA on the restenosis process (12).

After power calculations based on the assumption of a 40% relative reduction of an assumed 30% restenosis rate per patient in the placebo group, 500 patients accepted for elective PTCA were randomised 2 weeks prior to the procedure to 5.1 g/day of EPA+DHA (3 capsules twice daily of Omacor®, Pronova, Norway) or equal amont of corn oil as placebo. The primary end point was the rate of restenosis by quantitative coronary angiography performed after 6 months. Again the serum profile of fatty acids was determined in all patients at baseline and end of the study to document compliance with the study drugs.

Results

Of the 500 randomised patients 5 were disqualified before the PTCA and 103 during the PTCA procedure, the main reason for the latter being indication for stenting which was introduced methodologically during the study period. Four patients died during the study period, leaving 388 patients evaluable for the primary end point, 196 in the Omacor group and 192 in the placebo group. The number of evaluable stenoses was 266 and 263, respectively.

Restenosis according to the angiographic definitions in the study protocol occurred in 108/266 (40.6%) of the treated stenoses in the Omacor group and in 93/263 (35.4%) in the placebo group (OR 1.25, 95%CI 0.87-1.80, p=0.21). In the Omacor group one or more restenoses occurred in 90/196 (45.9%) patients as compared to 86/192 (44.8%) in the placebo group (OR 1.05, 95%CI 0.69-1.59, p=0.82).

Conclusion

We concluded that supplementation with 5.1g/day of highly concentrated PUFA for 6

months, initiated at least two weeks prior to PTCA, did not reduce the incidence of restenosis.

Substudies

Although the study was not powered for clinical end points, we also recorded some *clinical relevant data* (15). Thus, classification of the patients' angina pectoris according to the NYHA classification revealed similar distribution between the randomized groups at baseline with 40% in both groups in class II and 55% and 58% in class III in the Omacor and placebo groups, respectively. After 6 months, however, classification without knowledge of the randomized group revealed significantly more patients in classes III/IV in the Omacor group (22%) than in the placebo group (13%) (p=0.032 for differences between NYHA classes). This result was also in harmony with the use of antianginal drugs, which was similar in the groups at baseline. At follow-up after 6 months, the use of nitrates was more frequent in the Omacor group (28%) than in the placebo group (18%) (p=0.015). A difference of borderline significance was also found with regard to the use of β-blockers with 39% in the Omacor group and 30% in the placebo group (p=0.095) (Table 1).

Thus, if any effect of the high doses of PUFA in the CART study, our suggestion was that it might have been "negative".

In order to further elucidate potential mechanisms for the lack of a positive effect in line with the study hypothesis, we also performed additional substudies.

Table 1. The clinical status before and after intervention in the randomised groups in the CART-study Proportions of patients are given.

	Baseline		6 months		
Angina pectoris NYHA-class	Omacor	Placebo	Omacor	Placebo	p
I	5	5	51	52	
II	40	40	27	35	
III	55	58	22	13	**0.032**
Anti-anginal drugs					
Nitrates	72	70	28	18	**0.015**
Beta-blockers	76	73	39	30	**0.095**

p-values refer to differences between the groups at 6 months

The "post-CART" substudies

Taking advantage of the randomised design in the CART study we recruited 54 consecutive patients into a continued study after the follow-up examination at 6 months. Twenty-three of the patients had been on the PUFA supplementation for 6 months (group I) and 31 had taken placebo (group II). All patients were then given PUFA supplementation in the same dose as group I (5.1 g/day) for another 4 weeks.

A) Blood samples were drawn before and at the end of this study period for analyses of biochemical markers of endothelial function (tissue plasminogen activator antigen (tPAag), von Willebrand factor (vWF), the soluble forms of thrombomodulin (TM), P-selectin, E-selectin and vascular cell adhesion molecule-1 (VCAM-1)), as well as markers of peroxidation (vitamin E, and thio-barbituric-acid-reactive substances (TBARS)).

Results

At baseline, significant differences between the groups were found with lower median values of vWF (128% vs. 147%) and TM (24.9 vs. 32.5 ng/ml), but higher median values of E-selectin (41.4 vs. 35.5 ng/ml) and VCAM-1 (573 vs. 473 ng/ml) in group I. During the study period differences in changes between the groups were found; tPAag and TM decreased (p= 0.001 and p= 0.015, respectively, for difference between the groups), whereas E-selectin and VCAM-1 increased ($p < 0.01$ for both, for difference between the groups) in group II relative to group I (Figure 2). A parallel increase in TBARS and decrease in vitamin E was also seen in group II.

Conclusion

Our results indicate that the present formula and dose of PUFA supplementation decreases hemostatic markers of of atherosclerosis, whereas markers of inflammation may increase.

The latter may be the result of lipid peroxidation (16).

B) Twenty-three of the above-mentioned patients in the CART substudy after 6 months were randomly included in this substudy to evaluate procoagulant activity and cytokine expression in whole blood cultures with and without stimulation with LPS. Eleven patients had received PUFA supplementation (group I) and 12 patients had taken placebo (group II) at this study entrance. Analyses were performed at baseline and after 4 weeks of supplementation with PUFA.

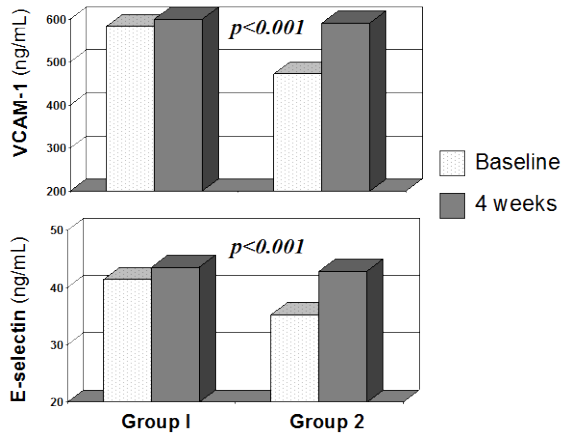

Figure 2. Endothelial cell markers in the "Post-CART study".
Group 1: Patients being on n-3 PUFA (5.1 g/d) throughout; Group 2: placebo at baseline and 4 weeks supplementation with n-3 PUFA (5.1 g/d). p-values refer to differences in changes between the groups.

Results

At baseline significantly lower levels of LPS-induced prothrombin fragment 1+2 were found in group I (p=0.01), this difference being eliminated after 4 weeks. LPS-induced IL-6 and TNFα were significantly higher at baseline in group I, and the differences in changes from baseline between the groups were highly significant with increasing values in group II (IL-6 p=0.001, TNFα p=0.002).

Conclusion

The present results indicate a beneficial reduction in pro-thrombotic potential in patients receiving high amounts of highly concentrated PUFA, whereas some proinflammatory responses might be adverse. The results seem to be in line with the results of Substudy A (23).

IS THE PROINFLAMMATORY EFFECT OF HIGH DOSES OF PUFA CONCENTRATES OBSERVED IN 2. COUNTERACTED BY ADDITIVE SUPPLEMENTATION WITH THE ANTIOXIDATIVE VITAMIN E?

Background

It is well known that the highly unsaturated very long chain fatty acids have an inherent proneness to peroxidation thereby taking actively part in peroxidative chain reactions interfering with the in vivo balance of oxidation and the antioxidative buffer capacity. Therefore, the commercially available concentrates of PUFA are regularly added low amounts of α-tocopherol to stabilize the product. However, this small amount will probably not play any important role in vivo.

In the CART study with the presented substudies a possible deleterious effect of the high amount (5.1 g/day) of highly concentrated PUFA supplementation was noted, and the results were thought to be mediated through peroxidation of the fatty acids visualized by an increase in TBARS and a decrease in circulating vitamin E levels.

Design of study

On this background the Omega-3 Fatty Acids and Vitamin E Study (OVITES) was designed with the purpose to investigate the effects of low and high doses of PUFA, the latter with and without supplementation of vitamin E, on soluble markers of inflammation and peroxidation in a population at risk for atherosclerosis.

Sixty-three non-diabetic men ≥ 40 years without known cardiovascular disease and without use of medication, but with total cholesterol values between 6 and 9 mmol/l, were recruited. They were randomly assigned to 6 weeks supplementation with either 0.85 g/day (group I) or 5.1 g/day of EPA+DHA (group II)(Omacor®, Pronova, Norway), or the latter amount of PUFA plus vitamin E 400mg/day (group III)(IDO-E, Pharmacia Upjohn, Norway). Blood samples were drawn before and at the end of the 6 weeks supplementation, and analysed for circulating markers of endothelial function (E-selectin, P-selectin, VCAM-1, ICAM-1, tPAag, vWF, TM), inflammation (CRP, IL-6, TNFα), and peroxidation (TBARS). Compliance with the n-3 PUFA supplementation was assessed by examination of the serum fatty acid profile.

Results

In group I no significant changes were noticed during the study period. In group II significantly increased values of E-selectin, VCAM-1, IL-6 and TNFα, as well as of TBARS were noted. A similar pattern was observed in group III with significantly increased values of E-selectin, VCAM-I and TNFα. However in group III no increase in TBARS was found (Figure 3).

Conclusion

The present results seem to confirm our findings in the CART studies that very high doses (5.1g/day of EPA+DHA) of highly concentrated PUFA may induce a proinflammatory response in individuals at risk for atherosclerotic disease and possibly being under a certain degree of oxidative stress. This effect is possibly brought about by lipid peroxidation. However, although supplementation with vitamin E seems to counteract the increase in circulating levels of TBARS, it did not counteract the influence of high doses of PUFA on circulating levels of proinflammatory cytokines and adhesion molecules (1).

HAS THE INCREASING REPLACEMENT BY VEGETABLE OILS FOR FISH OILS IN THE FEEDING OF FARMED SALMON ANY MEASURABLE EFFECTS IN HUMANS WITH ATHEROSCLEROTIC CORONARY HEART DISEASE?

Background

Given the present evidence of the very long-chain marine PUFA as important constituents of a healthy diet in relation to atherothrombotic disease states, fatty sea fish has been focused as optimal natural sources, and salmon is one of the main contributors. Because of relative shortness of wild-type salmon in relation to the steadily increasing demand, the international market of salmon is today totally dominated by farmed fish representing about 98%. Again, shortness of fish oil, mainly from sardines in southern sea locations, has necessitated experiments with vegetable oils to replace fish oils in the feed of farmed salmon. Thus, most of the salmon on the market today is fed on an approximately 50/50% mixture of fish oil and vegetable oil, for instance rapeseed oil. From analyses of the fillets of farmed salmon it has been documented that the profile of the fatty acids in the feed was reproduced in the fillets after a certain feeding period (24).

Design of study

On this background we designed the so-called “Fiord-to-table” study (22), where patients with stable angiographically documented coronary heart disease were randomised to one of three “arms” with dietary intake of 700g/week of differently fed farmed salmon for 6 weeks. The 3 prototypes of feed were: 100% fish oil (group I), 100% rapeseed oil (group II), and 50/50% fish oil and rapeseed oil (group III). With a fish weight about 3 kg they were slaugthered and the fillets were identified with different colours. Samples of the fillets were analysed for their fatty acid profile, and the bulk of fillets were transported in “freeze containers” to the hospital kitchen where delicate dinner products were made and introduced to the patients by a nutritionist. Sixty patients were enrolled in the study and 58 were available for the outcome analyses, 20 in group I and 19 in each of groups II and III. Blood samples were drawn at baseline and at the end of the study period. In addition to the fatty acid profile in serum, circulating levels of markers of vascular inflammation and peroxidation were determined.

Results

At baseline the groups were comparable with regard to demographic characteristics, use of relevant medication, serum fatty acid profile, serum lipoproteins and the outcome markers of inflammation and peroxidation. After 6 weeks intervention the serum fatty acid profile had changed significantly with signifcant changes also between the study groups. Thus, the pattern mirrored the different patterns in the salmon fillets, and therefore also those of the feeding pellets. The differences in changes from baseline were statistically significant for the increase in EPA, DHA, the sum of n-3 PUFA and the n-3/n-6 ratio in group I when compared to groups II and III, with intermediate results in group II (Figure 4). In addition a highly significant reduction in serum triglycerides was observed in group I ($p=0.002$) in contrast to the other groups.

Regarding the markers of inflammation, a highly significant decrease in VCAM-1 and a decrease of borderline significance in IL-6 and TNFα were recorded in group I, a decrease in TNFα also in group II, but with no changes in group III. The difference in changes from baseline between the groups were significant for

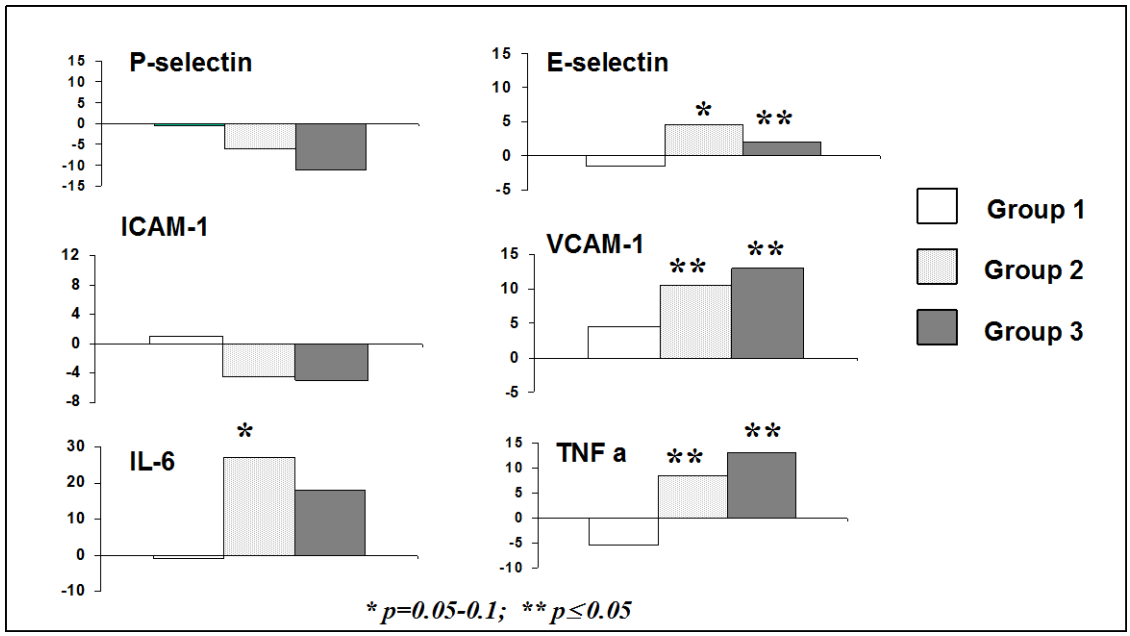

Figure 3. Percent changes in inflammatory markers in the 3 groups in the OVITES-study. p-values refer to differences in relative changes from baseline between groups; group 1 as reference.

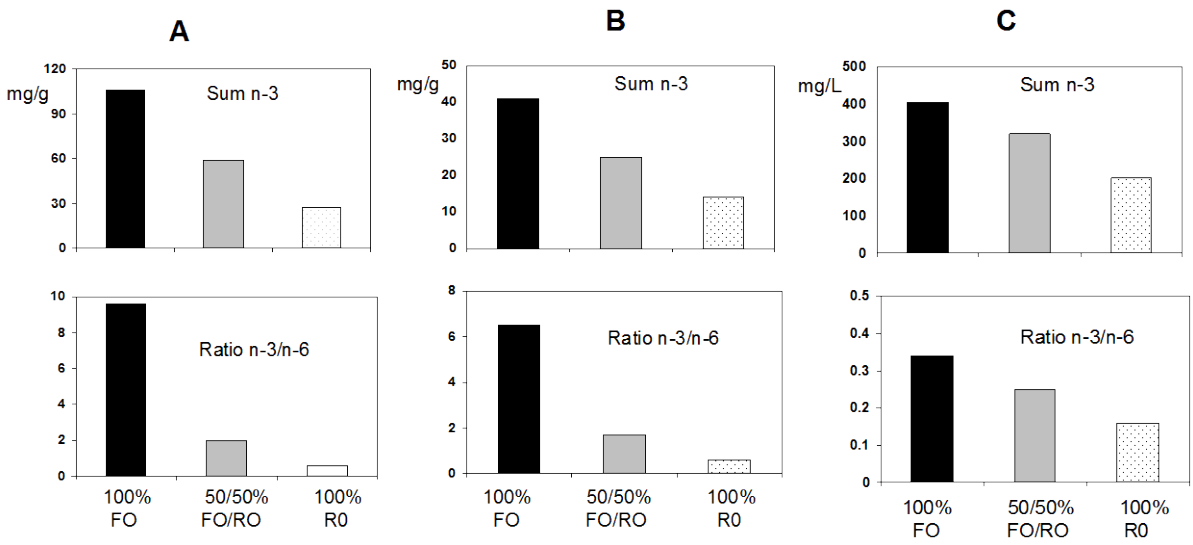

Figure 4. The patterns of the sum of n-3 FA and the ratio n-3/n-6 FA in the 3 different feeds (A), the corresponding salmon fillets (B), and the serum fatty acids in patients after the 6 weeks dietary intervention (C) in the "Fiord to Table"-study.

VCAM-1 and IL-6, with both being more pronounced in group I as compared to groups II and III ($p \leq 0.02$ for all). No changes in TBARS and vitamin E were noted in any of the study groups during the intervention.

Conclusion

We concluded that the fatty acid profiles of the salmon fillets, which mirrored those of their feeds, were mirrored also in the serum fatty acid profiles of the participating patients with CHD after 6 weeks of dietary intervention with 700 g/week of farmed Atlantic salmon. Furthermore, favourable changes in serum triglycerides and some markers of atherosclerotic activity were observed after ingestion of farmed salmon with high levels of marine n-3 PUFA when compared to ingestion of salmon fillets with intermediate and low content of marine n-3 PUFA, when replaced by rapeseed oil.

GENERAL COMMENTARY

Although dominating evidence exist in favour of a preventive effect of very long-chain marine PUFA for atherothrombotic cardiovascular disease states, large differences seem to exist between different populations intake of these PUFA in their ordinary diet. The rather extreme intake of more than 10g/day in Greenland Eskimoes is opposed to almost zero intake in some inland states of the US with an estimated mean of about 0.2g/d. Corresponding values are about 0.4g/day in Norway and 0.8-1.5g/day in Japan. Thus, the effect of supplementation of marine PUFA might be suggested also to vary greatly among various populations worldwide. In addition, the basic diet also differs largely, and it has been focused on the ratio between n-6 and n-3 fatty acids, in addition to the ratio of saturated and unsaturated fat. When supplementation of the very long-chain PUFA is recommended, the dose and formulation of supplementation have also been debated.

The aims or questions raised in the present review might be adressed as follows:

1. Yes, the supplementation of 3.4 g/day of highly concentrated very-long-chain marine PUFA (EPA+DHA, 2:1) in capsules does reduce the occlusion rates of aortocoronary venous bypass grafts significantly, and this effect is correlated to the change in serum levels of the sum of n-3 fatty acids, as well as to the change in the levels of EPA and DHA separately. Therefore, patients undergoing aortocoronary bypass surgery including venous grafts should be encouraged to keep a high dietary intake of marine n-3 fatty acids.

2. No, high amounts (≥ 5 g/day) of concentrates of very-long chain marine PUFA does not reduce the incidence of restenosis after percutaneous transluminal coronary angioplasty. If anything, such high amounts may induce a proinflammatory reaction, which might even be harmful. In parallel with the CART study, two large randomized trials with very similar protocols were conducted with similar negative results (17,4).

The mechanism by which a potentially proinflammatory and harmful effect of large amounts of PUFA is probably through peroxidation. The production of free oxygen radicals is known to activate the transcription factor NFκB, the key transcription factor in proinflammatory responses. While the actual fatty acids themselves are natural ligands of the PPARs and thereby mainly induce anti-inflammatory responses, the potential activation of NFκB might change this balance in a proinflammatory direction (Figure 5). The results of the CART substudies might give support to this hypothesis.

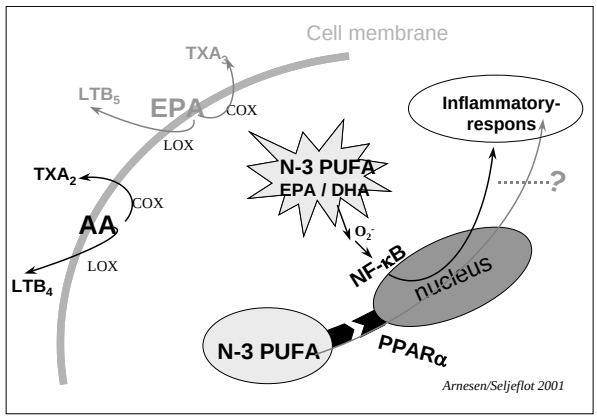

Figure 5. Potential mechanisms by which n-3 PUFAs exert both anti-inflammatory (through PPAR-activation) and pro-inflammatory effects (through NF-kB avtivation).

3. No, the additive supplementation of 400mg/day of vitamin E does not counteract the proinflammatory effect of high doses of very-long chain marine PUFA in patients with hypercholesterolemia, although the increase in the peroxidative product TBARS in the circulation is reduced. These results might be in line with the negative results of randomized

clinical trials with vitamin E supplementation in patients with atherosclerotic disease states (13).

The antioxidative effects of vitamin E is probably mainly taking place in the circulation or water phases in the organism, whereas the relevant peroxidation and potential activation of NFκB are intracellular processes where other antioxidative buffer systems play a major role. The latter systems might have reduced capacity in individuals under oxidative stress like patients with or at risk for atherothrombotic disease states. Whether these mechanisms are operative also when high amounts of very-long chain marine PUFA are ingested in its natural form as fatty fish is an unresolved question. However, no influence on the level of circulating TBARS or vitamin E could be observed in the "Fiord-to-table" trial.

4. Yes, the replacement of fish oils by vegetable oils like rapeseed oil in the feed of farmed Atlantic salmon might influence the disease state in patients with atherosclerotic CHD. When patients (and their close families) were administered a diet with 5 major meals with a sum of 700 g/week with differently fed Atlantic salmon for 6 weeks, their profile of serum fatty acids were mirroring the profiles of the salmon fillets and the feed of the salmon. In other words "the patients become what the salmon eat". In this experimental set-up, a reduced proinflammatory profile was observed in the circulation of the patients who were eating the salmon fed on 100% fish oil, whereas this was not the case when fish oil was replaced by rapeseed oil. Of course, due to the number of patients and the limited intervention period, no clinical evaluation was performed. Nevertheless, the measured inflammatory markers, being improved in the present study, have been associated with reduced risk of morbidity and mortality of cardiovascular disease (18,3,9).

Further studies of longer duration, and possibly with somewhat reduced amounts of fatty fish/week, more in line with recommendations of at least 2 meals of fatty fish/week, should preferably be undertaken to consolidate the present findings.

Other articles in this theme issue include references (27-38).

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