Relation of Fish Oil Supplementation to Markers of Atherothrombotic Risk in Patients With Cardiovascular Disease Not Receiving Lipid-Lowering Therapy

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Fish oil supplementation (FOS) is known to have cardiovascular benefits. However, the effects of FOS on thrombosis are incompletely understood. We sought to determine if the use of FOS is associated with lower indices of atherothrombotic risk in patients with suspected coronary artery disease (sCAD). This is a subgroup analysis of consecutive patients with sCAD (n = 600) enrolled in the Multi-Analyte, Thrombogenic, and Genetic Markers of Atherosclerosis study. Patients on FOS were compared with patients not on FOS. Lipid profile was determined by vertical density gradient ultracentrifugation (n = 520), eicosapentaenoic acid + docosahexaenoic acid was measured by gas chromatography (n = 437), and AtherOx testing was performed by immunoassay (n = 343). Thromboelastography (n = 419), ADP- and collagen-induced platelet aggregation (n = 137), and urinary 11-dehydrothromboxane B_2 levels (n = 259) were performed immediately before elective coronary angiography. In the total population, FOS was associated with higher eicosapentaenoic acid + docosahexaenoic acid content ($p < 0.001$), lower triglycerides ($p = 0.04$), total very low−density lipoprotein cholesterol ($p = 0.002$), intermediate-density lipoprotein cholesterol ($p = 0.02$), and AtherOx levels ($p = 0.02$) but not in patients on lipid-lowering therapy. Patients not on lipid-lowering therapy taking FOS had lower very low−density lipoprotein cholesterol, intermediate-density lipoprotein cholesterol, remnant lipoproteins, triglycerides, low-density lipoprotein cholesterol, AtherOx levels, collagen-induced platelet aggregation, thrombin-induced platelet-fibrin clot strength, and shear elasticity ($p < 0.03$ for all). In clopidogrel-treated patients, there was no difference in ADP-induced aggregation between FOS groups. Patients on FOS had lower urinary 11-dehydrothromboxane B_2 levels regardless of lipid-lowering therapy ($p < 0.04$). In conclusion, the findings of this study support the potential benefit of FOS for atherothrombotic risk reduction in sCAD with the greatest benefit in patients not receiving lipid-lowering therapy. Future prospective studies to compare FOS with lipid-lowering therapy and to assess the independent effects of FOS on thrombogenicity are needed. **(Am J Cardiol 2015;115:1204−1211)**

The effects of fish oil supplementation (FOS) on thrombosis are inconsistent and not well understood. Polyunsaturated fatty acids (PUFAs) compete with arachidonic acid (AA) for esterification into platelet membrane phospholipids and act as substrates for cyclo-oxygenase and lipoxygenase. The net effect of these reactions is reduced synthesis of AA-derived eicosanoids and increased synthesis of n-3 (Omega-3) PUFA eicosanoids (Figure 1).[1,2] The production of less biologically active n-3 PUFA derivatives (i.e., prostaglandin-E_3 and thromboxane-A_3) compared with proinflammatory and/or prothrombotic AA derivatives (i.e., prostaglandin-E_2 and thromboxane-A_2) may contribute to reduced platelet activation and reduced tendency for thrombosis with FOS.[3,4] However, the inhibition of pro-aggregatory thromboxane biosynthesis by n-3 PUFA is thought to be of marginal significance, and well below that which is produced by low-dose aspirin therapy, suggesting that any reduction in platelet function is most likely the product of a different mechanism.[5] In this study, we sought to ascertain if use of FOS was associated with a reduced overall atherothrombotic risk profile in patients with suspected coronary artery disease (sCAD) by measuring lipid levels and markers of thrombogenicity simultaneously.

Methods

This is an observational case series study that compares use of FOS in various subgroups. After approval and written informed consent from the institutional review board, 600

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See page 1210 for disclosure information.

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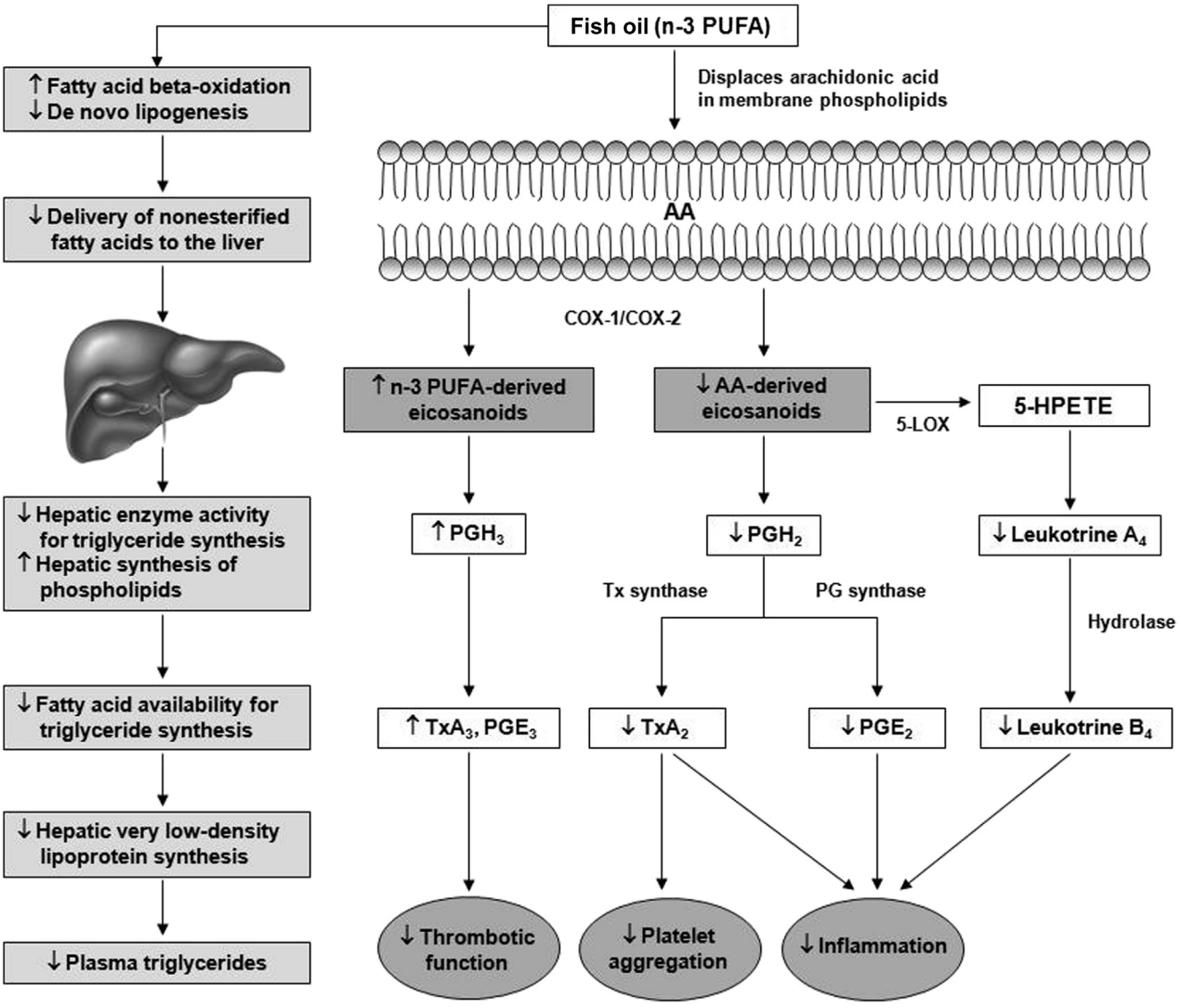

Figure 1. n-3 PUFA mechanism of action on lipids, thrombogenicity, and inflammation.

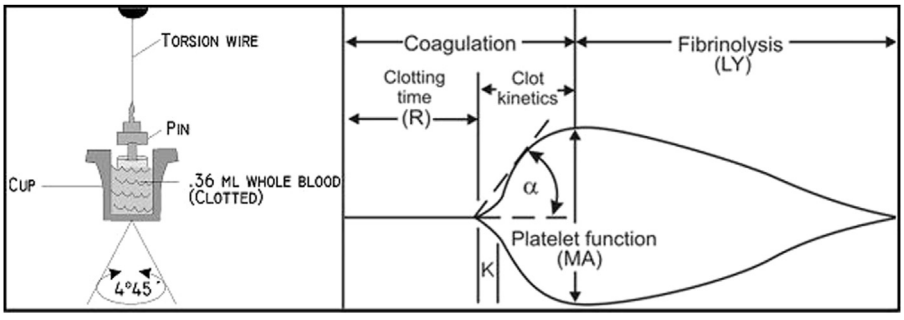

Figure 2. Schematic of TEG system. A torsion wire suspends a pin that is immersed in blood. As the clot forms while the cup is rotated 45°, the pin will rotate depending on the strength of the fibrin-platelet bonds. Signal is discharged continuously and reflects the clotting process.

consecutive patients with sCAD on daily 325 mg aspirin therapy were enrolled before elective cardiac catheterization in the Multi-Analyte, Thrombogenic, and Genetic Markers of Atherosclerosis study (NCT01276678) from July 2010 to December 2013. Patients were referred for cardiac catheterization for the following reasons: (1) a positive stress test with no angina, (2) a positive stress test with classic angina, and/or (3) a positive computed tomographic scan. Patients were excluded from the study for any of the following reasons: pregnancy, acute infection, experimental