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Canola oil decreases cholesterol and improves endothelial function in patients with peripheral arterial occlusive disease — a pilot study☆

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Summary *Background:* Dietary supplementation with omega-3 PUFAs has been shown to reduce cardiovascular morbidity and mortality. This pilot study investigated the effects of supplementation with plant-derived omega-3 and omega-6 PUFAs in patients with atherosclerosis.
Methods: Forty patients with PAD supplemented their usual diet with 2 tablespoons/day of canola oil ($n = 20$) or sunflower oil ($n = 20$), containing 2.24 g of α-linolenic acid or 16.24 g of linoleic acid, respectively, for 8 weeks. Laser Doppler flux (LDF), was assessed at rest and during reactive hyperaemia. Other measurements included parameters of heart rate variability (HRV), markers of plasmatic coagulation, fibrinolysis, platelet activation, inflammation, and lipid and homocysteine levels.
Results: Despite randomization, baseline values for LDF and HRV differed between the two groups. LDL-cholesterol decreased (from 2.74 ± 0.73 to 2.42 ± 0.65 mmol/L, $p = 0.007$) with canola oil but not with sunflower oil. The difference in the percent increase of LDF after ischemic challenge increased with canola oil from a median (25th; 75th percentiles) of 75.2% (48.6; 161.2) to 151.7% (117.8; 260.0) ($p = 0.008$) and with sunflower oil from 157.9% (125.4; 229.8) to 178.6% (127.3; 356.3) ($p = 0.03$), whereas a control group did show no change. HRV and other markers did not change.

Abbreviations: %RR50, the percent difference between adjacent RR intervals that were greater than 50 msec; ALA, α-linolenic acid; DHA, docosapentaneoic acid; DD, D-dimers; EPA, eicosapentaneoic acid; F1 + 2, prothrombin fragment 1 + 2; FMD, flow-mediated dilation; GISSI, gruppo italiano per lo studio della sopravvivenza nell'infarto miocardio; LA, linoleic acid; LDF, laser Doppler flow; NO, nitric oxide; PAD, peripheral artery occlusive disease; PAI-1, plasminogen activator inhibitor-1; PUFA, polyunsaturated fatty acid; rmsSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals; SDANN, the standard deviation of the normal RR intervals averaged over 5 min intervals during the monitoring period; SDNN, the standard deviation of all normal RR intervals observed over the monitoring period; TAT, thombin-antithrombin complex; t-PA, tissue-type plasminogen activator.

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Conclusions: Canola oil containing omega-3 PUFAs may confer cardiovascular protection by improving endothelial function and lowering LDL-cholesterol, but additional studies are warranted.

Introduction

Interventions that increase the amount of dietary omega-3 fatty acids have become an important issue in primary[1] and secondary[2] prevention of cardiovascular disease. Evidence from epidemiological studies and results from interventional trials have led to recommendations concerning the intake of omega-3 PUFAs for people with and without coronary heart disease.[3] However, a recent metaanalysis cast doubts on the efficacy of such intervention:[4] interventional study data is difficult to interpret due to the complexity of dietary interventions (e.g. the difficulty of attributing an effect to a single substance and the possible toxic effects of fish contaminants), and due to interactions/confounding factors (e.g. the interaction between marine and plant-based omega-3 PUFAs).[5–7] Moreover, the mechanism(s) by which omega-3 PUFAs exert their biological effects are not fully understood, but may include hypolipemic, antiatherothrombotic, antiarrhythmic, and anti-inflammatory effects, as well as effects on endothelial function.[8]

Among the omega-3 PUFAs, plant-based ALA has been used in fewer interventional studies than marine-based omega-3 PUFAs such as EPA (C20:5n-3) and DHA (C22:6n-3).[4] By desaturation and elongation ALA provides the substrates for vasodilating and antiaggregant prostaglandins and is a precursor for long-chain EPA and, to a lesser extent, for DHA;[9] the increase in EPA levels following an ALA-rich diet, however, has been found to be modest.[10] From epidemiological and interventional studies, however, it is unclear whether ALA confers benefits similar to marine-based omega-3 PUFAs for primary and secondary prevention of cardiovascular disease.[11] The Western diet typically contains much more omega-6 than omega-3 PUFAs, which leads to a non-physiological omega-6:omega-3 balance and to production of interleukin-1, prostaglandins, and leukotrienes.[2] Thus, plant-based LA, which is widely consumed in vegetable oils as a recommended substitute for saturated fats, is an omega-6 PUFA and a substrate for prostaglandins with inflammatory, vasoconstricting, and proaggregant properties.[8,12]

Surrogate markers commonly used to assess the effect of interventions on cardiovascular disease include markers of coagulation, platelet reactivity, inflammation, serum lipids, and homocysteine [Hcy].[13–15] Available data on changes in these markers in response to increasing the amount of dietary omega-3 PUFAs are conflicting.[6,11,16–22] Endothelial dysfunction, which is closely related to adverse cardiovascular events and is felt to be a sensitive marker of atherosclerosis,[23] has also been assessed in the setting of dietary interventions with fatty acid supplementation.[23,24] Moreover, the omega-3 PUFAs could exert a positive effect on arrhythmia, as has been suggested in the GISSI trial which showed a reduction in the number of sudden cardiac deaths.[25]

After considering all these data, we performed an interventional pilot study in patients with chronic PAD by adding canola (containing ALA) or sunflower oil (containing LA) to their usual diet. We analyzed surrogate endpoints, including parameters of atherothrombosis, fibrinolysis, inflammation, blood lipids, endothelial function, and heart rate variability.

Methods

Forty Caucasian patients, at least 50 years old with chronic PAD (defined as an ankle-brachial index <0.9 plus a duplex- or angiographically-based verification of a $>50\%$ stenosis or occlusion in a leg artery), were randomized in blocks of four (http://www.randomization.com). Exclusion criteria were acute, intercurrent illness; thromboangiitis obliterans; renal insufficiency (creatinine >130 μmol/L); acute myocardial infarction or stroke within 2 months; current oral anticoagulation medication; liver cirrhosis; and presence of an active malignant tumour. All participants were instructed not to change their habitual alimentation, which was supplemented in a blinded fashion with 2 tablespoons/day of vegetal oil taken without any additional serving. Group A ($n = 20$) received 2 tablespoons/day of canola oil, corresponding to a daily intake of 2.24 g of ALA (C18:3n-3; data from Sabo laboratory, Manno, Switzerland), and group B received 2 tablespoons/day of sunflower oil, corresponding to a daily intake of 16.24 g of LA acid (C18:2n-6). The oils were commercially available from Migros/Sabo oil (Manno, Switzerland), were packaged in similar bottles, and were filtered in a way that rendered them visually indistinguishable. Patients and doctors were blinded as to the contents of the bottles. The study period was 8 weeks, and compliance was assessed by the return of empty bottles. At baseline and at the end of the study, blood was drawn from an antecubital vein between 8 and 9 a.m. after 15 min of rest in a supine position. Blood was collected in a 10 ml plastic syringe (Monovette, Sarstedt, Nümbrecht, Germany) containing 1 ml 0.106 M trisodium citrate; blood samples were immediately placed on melting ice. Plasma was separated by cold centrifugation, and aliquots were stored at $-70\,^{\circ}C$ until processing.

F 1 + 2 and TAT, both markers for thrombin generation, were measured by ELISA (Enzygnost F 1 + 2; Dade Behring, Marburg, Germany). DD, by-products of fibrinolysis, were also measured by ELISA (miniVidas by bioMérieux, Lyon, France). t-PA and PAI-1 were measured by ELISA (Hyphen Biomed, Neuville-sur-Oise France and Biopool, Umea, Sweden, respectively). Soluble CD40L [sCD40L], a marker of platelet activation, was determined by ELISA (Biosource, Camarillo, CA, USA). Plasma Hcy was determined by high-performance liquid chromatography and fluorescence detection. Ultrasensitive CRP was measured by nephelometry