Liposomal docosahexaenoic acid halts atherosclerosis progression


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Background: Atherosclerosis is the main cause underlying cardiovascular disease (CVD). Docosahexaenoic acid (DHA, 22:6n-3) is a hydrophobic polyunsaturated fatty acid that exerts anti-inflammatory and antioxidant activities. However, the beneficial effects of DHA on CVD have been controversial likely due to variations in bioavailability after oral intake.

Purpose: In this study, we aim to investigate the potential inhibiting properties of liposomal DHA on atherosclerosis progression upon intravenous administration.

Methods: Four weeks old ApoE−/− and LDLr−/− mice were fed on athero-inducing high fat diet for 4 weeks and then randomly divided into two groups. The mice received either control liposomes (control group) or liposomes containing DHA (liposomal DHA treatment group) via intravenous injection, twice a week for 8 weeks while still being fed on high fat diet. At the experiment endpoint, whole aortas were collected for Oil Red O staining to quantify plaque area or for biochemical analysis. Plasma was collected for total cholesterol measurement and lipidomic analysis. Aortic roots were used for histological analysis.

Results: Upon intravenous injection, as shown by IVIS imaging, DHA-containing liposomes accumulated preferentially in the atherosclerotic plaques. Compared to control liposomes, liposomal DHA treatment reduced the atherosclerotic plaque area in both atherosclerosis animal models, with the total plaque area decreased by 35.8% in ApoE−/− mice, (p<0.001) and by 22.4% in LDLr−/− mice (p<0.05). Plaque composition analysis revealed that liposomal DHA treatment increased collagen content and reduced the number of macrophages and neutral lipid within the plaques, resulting in a lower plaque vulnerability index (1.095 for liposomal DHA treated group vs. 1.692 for control group, p<0.05). Among those plaque macrophages, as demonstrated by immunohistology, M2 (anti-inflammatory) macrophages accounted for 4.44% in liposomal DHA treated mice and 2.24% in control liposomes treated mice (p<0.05). In agreement with the histology results, higher mRNA expression levels of anti-inflammatory markers (IL-10, CD206 and CD163) and collagen type 1 were determined in aortic tissue after liposomal DHA treatment. Moreover, liposomal DHA did not change total cholesterol level in the blood but significantly lowered plasma levels of several species of triglycerides. In vitro experiment with bone marrow derived macrophages showed that liposomal DHA was able to suppress lipopolysaccharide-induced inflammatory response and oxidative stress.

Conclusions: Our findings demonstrate that incorporation of DHA in injectable liposomes is an effective way to increase the inhibitory effects of DHA on halting the progression of atherosclerosis via lowering circulating triglycerides, reducing plaque inflammation, and enhancing plaque stability. Intravenous administration of liposomal DHA may become an efficacious strategy for the treatment of atherosclerosis.