Dietary docosahexaenoic acid (DHA) halts progression of nonalcoholic steatohepatitis (NASH), but does not promote fibrosis remission in Ldlr⁻/⁻ mice.

Kelli A. Lytle, Carmen Wong and Donald B. Jump
Nutrition Program BPHS-Oregon State University and the Linus Pauling Institute.

Nonalcoholic fatty liver disease (NAFLD) is a major public health concern. NASH, the progressive form of NAFLD, is characterized by hepatosteatosis, inflammation, oxidative stress and fibrosis. NASH is a risk factor for cirrhosis, hepatocellular carcinoma and liver failure. We previously established that DHA attenuated the onset of western diet (WD)-induced NASH in Ldlr⁻/⁻ mice. Herein, we evaluate the efficacy of DHA to slow progression and promote disease remission in mice with pre-existing NASH. Mice maintained on the WD for 22 weeks developed mild NASH. These mice were randomized to 3 groups: (Group 1) WD-Base [euthanized at 22 wks]; (Group 2) WD + Olive oil; and (Group 3) WD + DHA. Olive oil was added to ensure isocaloric diets and DHA was at a therapeutic dose, i.e., 2% of total calories. A Control Group was maintained on laboratory chow for the duration of the study. Mice in Groups 2 and 3 were euthanized after 8 weeks on the new diets. DHA had no effect on WD-induced changes in body weight, food intake, plasma glucose, TLR4 agonists or leptin. DHA, however, decreased blood lipids (triglycerides, cholesterol) and Toll-like receptor 2 agonists. Analysis of hepatic histology, lipids and gene expression established that the NASH phenotype worsened in WD + Olive oil group, but not WD + DHA. Hepatic gene expression markers of inflammation, oxidative stress and fibrosis in the WD-Base and WD + DHA groups were comparable. While DHA supplementation increased hepatic omega-3 fatty acids and repressed further total hepatic fatty acid accumulation, it failed to fully eliminate fibrosis. Taken together, these studies establish that DHA supplementation, at physiologically relevant levels, attenuates disease progression in mice with pre-established NASH, but does not promote full NASH remission.

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