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COMMENTARY

Omega 3 Fatty Acid Supplements and Cardiovascular Health

Commentary on the article by de Jong *et al.* on page 411

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Breastfeeding is associated with lower blood pressure (BP) in offspring than formula feeding (1). One postulated mechanism for this benefit relates to the fatty acids in breast milk that include omega-3 and omega-6 long-chain polyunsaturated fatty acids (LCPUFA). Until recently, infant formulas did not contain LCPUFA.

There is strong evidence from clinical, experimental, and epidemiological studies that long-chain omega-3 fatty acids derived from fish and fish oil [eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)] reduce cardiovascular disease (2). Numerous prospective studies have shown a relationship between fish consumption and a lower incidence of coronary disease, mortality, and sudden death, and meta-analyses have shown that fish oil is protective for coronary heart disease mortality. In addition, randomized controlled trials in individuals with established coronary disease or heart failure have shown that increased intake of omega-3 fatty acids protects against atherosclerotic heart disease and sudden coronary death. The benefits of omega-3 fatty acids likely relate to their effects on a wide range of cardiovascular biomarkers and risk factors including BP, cardiac function, arterial compliance, inflammatory markers, triglycerides, HDL-cholesterol, adipokines, and insulin (3). Our research group has also shown benefits of omega-3 fatty acids on oxidative stress, thrombotic factors, and platelet aggregation. Omega-3 fatty acids exert their effects by altering membrane structure and function, eicosanoid metabolism and action, and nuclear transcription factors regulating the gene expression.

In humans, there is strong evidence that consumption of omega-3 fatty acids reduces BP (4). Moreover, we have shown that the BP-lowering effects of omega-3 fatty acids were additive to weight reduction in overweight-treated hypertensives (5). Using 24-h ambulatory BP monitoring, omega-3 fatty acids + weight loss reduced daytime BP by 13.0/9.3 mm Hg compared with controls. BP decreased to 6.0/3.0 mm Hg with omega-3 fatty acids alone and 5.5/2.2 with weight loss alone, relative to controls. Awake heart rate was reduced by 1.8, 4.3, and 6.1 beats/min in the weight loss, omega-3 fatty acid, and weight loss + omega-3 fatty acid groups, respectively, relative to controls (5). In healthy adolescents (boys), dietary intakes of EPA and DHA have been inversely associated with BP (6).

We have shown that in overweight, mildly hypercholesterolemic adults, BP and heart rate are differentially affected by EPA and DHA (7). DHA, but not EPA, supplemented for 6 wk, significantly reduced 24-h BP (−5.8/−3.3 mm Hg), relative to a control oil. The BP changes with DHA were accompanied by significant improvements in endothelial and smooth muscle function and reduced vasoconstrictor responses in the forearm microcirculation (8). In addition, DHA, but not EPA, significantly reduced 24-h heart rate (7).

The BP reduction associated with omega-3 fatty acids is most likely related to improvements in endothelial function and arterial compliance, along with a cardiac effect mediated by a decrease in heart rate. Possible mechanisms include suppression of vasoconstrictor prostanoids, enhanced production and/or release of NO, reduced plasma noradrenalin, changes in calcium flux, increased membrane fluidity, effects related to potential antioxidant actions of omega-3 fatty acids, or the increase in HDL-C (4). Omega-3 fatty acids reduce heart rate, suggesting a significant cardiac component associated with the antihypertensive effects, possibly mediated by effects on cardiac myocytes, autonomic nerve function, or β-adrenoreceptor activity (4).

In animals, perinatal omega-3 fatty acid deficiency causes hypertension and the effect can be reversed by providing omega-3 fatty acids in the early postnatal period (9). The investigators showed that the effects on BP were related to hypothalamic concentration of DHA and that deficient rats consumed more water and salt than sufficient animals and thus hypothesized an abnormal control of osmotic sensors or angiotensin-related pathways and a critical period for the effect of DHA on BP.

Fetal programming is important in the development of hypertension with fetal glucocorticoids being a key mediator. Maternal dexamethasone treatment of rats during pregnancy

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leads to hypertension in offspring at 6 mo of age. The effect can be completely blocked by a diet high in omega-3 fatty acids leading to the hypothesis that dietary supplementation with omega-3 fatty acids may reduce programmed adverse outcomes such as hypertension in humans (10).

The Groningen LCPUFA study (11) published in this edition of *Pediatric Research* reported no effect of LCPUFA supplementation on cardiovascular outcomes of healthy children. The investigators reported outcomes at 9 y in a double-blind randomized trial in healthy term infants of formula supplemented with LCPUFA [omega-3 fatty acids (DHA) and omega-6 fatty acids (arachidonic acid, AA)] on BP, heart rate, and BMI. The authors aimed to mimic the beneficial effect of breastfeeding on reducing BP by adding LCPUFA to formula.

Outcomes of previous studies of omega-3 fatty acid supplementation in early life and cardiovascular risk are summarized by de Jong *et al.* (11). The evidence is conflicting with positive and negative results not dissimilar to the situation when trials of LCPUFA supplementation of infant formula with neurodevelopmental outcomes are analyzed (12). Meldrum *et al.* (13) reviewed factors to consider when interpreting the results from trials of LCPUFA supplementation in infants and these include dose, source and form of oil, duration of supplementation, sample size, genetic polymorphisms, and choice of outcome measures.

de Jong *et al.* have specified the dose (DHA and AA at 0.30% and 0.45% fatty acids), source (egg yolk, tuna oil, and single cell/fungal oil) and form of supplement (15% phospholipid and 85% triglycerides) in their formula. The supplement was chosen to mimic breast milk in dose and form. The dose of DHA was not high and EPA was very low. The duration of supplementation was short at 2 months and chosen as representative of Dutch breastfeeding duration. The authors acknowledge several limitations of their study. First, they had a substantial attrition rate (28%), and second, the study was underpowered. The authors state their sample size was able to detect a difference in BP of 1.5 mm Hg. A larger sample size and assessment of more sensitive markers of cardiovascular health may have demonstrated a benefit.

Prolonged supplementation has been assessed by Ayer *et al.*, (14) who reported BP and measurements of arterial structure and function at the age of 8 y after 5 y of an intervention from infancy, which increased dietary omega-3 fatty acids intakes several times above the recommended intake and reduced omega-6 intakes. No difference in BP and other cardiovascular outcomes were found between the groups. Over 400 children were assessed with sensitive markers including carotid artery distensibility and brachial pulse wave velocity.

One explanation for the lack of conclusive effects in trials of omega-3 fatty acid supplementation is that genetic differences may modulate the levels of LCPUFA. Fatty acid desaturases (*FADS 1* and *2*) are genes that are important in the metabolism of fatty acids, and there is some evidence that genetic variation in fatty acid metabolism moderates the effects of breastfeeding compared with formula feeding on neurocognitive development of children (15). This concept is sometimes referred to as "individualized nutrition" and implies that only subgroups with specific genetic polymorphisms will benefit from supplementation.

The effect that omega-3 fatty acid supplements may have on cardiovascular disease by reducing inflammation has received little attention but it is accepted that chronic inflammation is important in the pathogenesis of cardiovascular disease. The effect of lipid metabolites in resolving inflammation and their influence on later vascular disease has yet to be fully elucidated although it is an area of active research into potential benefits of omega-3 supplements (16).

The conclusions from the de Jong *et al.* (11) are consistent with meta-analyses in infancy (12) and provide little evidence that there is a benefit to term infants of supplementing formula with LCPUFA. However, future studies should focus on higher dose, longer duration, larger sample size, and selection of populations and outcomes specific to omega-3 fatty acids. Studies should also examine cardiovascular risk later in adolescence and adulthood. It is likely that using 24-h ambulatory BP monitoring will provide a more sensitive measure of BP. The differential effects of DHA and EPA in fish oil supplements also needs be clarified in infants, as does the effect of omega-3 fatty acids with and without omega-6 fatty acid supplements (DHA +/− AA).

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