Omega 3's -- more evidence for their benefit

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Omega-3 fatty acids –fats commonly found in fish oil – were shown several years ago to prevent retinopathy, a major form of blindness, in a mouse model of the disease. A follow-up study, from the same research team at Children's Hospital Boston, now reveals exactly how omega-3's provide protection, and provides reassurance that widely used COX-inhibiting drugs like aspirin and NSAIDs don't negate their benefit. The findings, published in the February 9th issue of *Science Translational Medicine,* also suggest that omega-3's may be beneficial in diabetes.

Retinopathy – an eye disease caused by the proliferation of tortuous, leaky blood vessels in the retina – is a leading cause of blindness, affecting 4.1 million Americans with diabetes (a number expected to double over the next 15 years) and many premature infants. Another 7 million-plus Americans have age-related macular degeneration (AMD); this too will increase as the population ages. The most common "wet" form of AMD is also caused by abnormal blood vessel growth.

The ability to prevent these "neovascular" eye diseases with omega-3 fatty acids could provide tremendous cost savings, says Children's ophthalmologist Lois Smith, MD, PhD, senior investigator on the study. "The cost of omega-3 supplementation is about $10 a month, versus up to $4,000 a month for anti-VEGF therapy," she says, referring to drugs such as Macugen and Lucentis used in AMD and diabetic retinopathy. "Our new findings give us new information on how omega-3s work that makes them an even more promising option."

Omega-3 fatty acids, highly concentrated in the retina, are often lacking

in Western diets, which tend to be higher in omega-6 fatty acids. In Smith's previous study, mice fed diets rich in omega-3 fatty acids by Smith's team had nearly 50 percent less pathologic vessel growth in the retina than mice fed omega-6-rich diets. Smith and colleagues further showed that the omega-3 diet decreased inflammatory messaging in the eye.

In the new study, they document another protective mechanism: a direct effect on blood vessel growth (angiogenesis) that selectively promotes the growth of healthy blood vessels and inhibits the growth of abnormal vessels.

In addition, Smith and colleagues isolated the specific compound from omega-3 fatty acids that has these beneficial effects in mice (a metabolite of the omega-3 fatty acid DHA, known as 4-HDHA), and the enzyme that produces it (5-lipoxygenase, or 5-LOX). They showed that COX enzymes are not involved in omega-3 breakdown, suggesting that aspirin and NSAIDs – taken by millions of Americans -- will not interfere with omega-3 benefits.

"This is important for people with diabetes, who often take aspirin to prevent heart disease, and also for elderly people with AMD who have a propensity for heart disease," says Smith. (One drug used for asthma, zileuton, does interfere with 5-LOX, however.)

Finally, the study demonstrated that 5-LOX acts by activating the PPAR-gamma receptor, the same receptor targeted by "glitazone" drugs such as Avandia, taken by patients with type 2 diabetes to increase their sensitivity to insulin. Since these drugs also increase the risk for heart disease, boosting omega-3 intake through diet or supplements might be a safer way to improve insulin sensitivity in patients with diabetes or pre-diabetes. "There needs to be a good clinical study in diabetes," Smith says.

Smith works closely with principal investigators at the National Eye Institute who are conducting an ongoing multicenter trial of omega-3 supplements in patients with AMD, known as AREDS2. The trial will continue until 2013. An earlier retrospective study, AREDS1, found higher self-reported intake of fish to be associated with a lower likelihood of AMD.

In addition, Smith is collaborating with a group in Sweden that is conducting a clinical trial of omega-3 fatty acids in premature infants, who are often deficient in omega-3. That study will measure infants' blood levels of omega-3 products and follow the infants to see if they develop retinopathy. If results are promising Smith will seek FDA approval to conduct a clinical trial in premature infants at Children's.

Meanwhile, in her lab work, Smith plans to continue seeking beneficial lipid pathways, while looking for the most harmful omega 6 metabolites. "We found the good guys, now we'll look for the bad ones," says Smith. "If we find the pathways, maybe we can selectively block the bad metabolites. We would hope to start with drugs that are already available."

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