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More Evidence that Maternal Long-Chain PUFAs Improve Infant Development

The biennial meeting of the International Society for the Study of Fatty Acids and Lipids (ISSFAL) in May provided splendid overviews of some of the hottest topics in fatty acid research. In some cases, fatty acids take a back seat to the focus on eicosanoid derivatives and mechanisms of action. Examples of this are new pathways in the resolution of inflammation involving lipoxins, resolvins and protectins, and the derivatives of cytochrome p450 enzymes known as “EETs” (epoxyeicosatrienoic acids). In clinical, immunological and nutritional areas much attention is paid not only to which long-chain polyunsaturated fatty acids (LC-PUFAs) and their derivatives are doing what, when and where, but how these fatty acids and products interact with proteins, genes, membrane receptors, hormones and drugs. There are now more studies on attention deficit hyperactivity disorder, mental health, maternal LC-PUFA supplementation during pregnancy, skin disorders, cancer and parenteral nutrition. So prolific is PUFA research that many papers must wait for the September issue.

Several reports on omega-3 (n-3) LC-PUFAs in maternal and infant health appear in this issue. Of particular note is the effect of higher levels of docosahexaenoic acid (DHA) and arachidonic acid (ARA) in very low birthweight infants than what is currently approved for use in the U.S. Providing DHA and ARA at 59 and 47 mg/day, respectively, to infants weighing less than 1,500 g (3.3 lb.) rather than the standard 32 and 22 mg/day, more closely resembles the amount of LC-PUFAs an infant would receive had it not been born early. Results at 6 months of age showed improved cognition in the supplemented infants compared with those given the usual level of LC-PUFAs.

In a report of Inuit mothers who consumed large amounts of fish and sea mammals during pregnancy, much of which carries appreciable levels of contaminants, higher prenatal DHA was associated with greater birthweight, gestational age and visual acuity in the infants at 6 months of age and higher mental and psychomotor developmental scores at 11 months of age. In spite of exposure to methylmercury and PCBs, high prenatal DHA was accompanied by better infant outcomes. Another study in infants of mothers exposed to contaminants from eating more than 2 fish servings/week during pregnancy reported significantly higher visual motor scores in the children at age 3 years compared with children whose mothers avoided eating fish. These studies do not justify ignoring contaminants in seafood, but they add to a large body of data indicating that the benefits of eating most species of fish during pregnancy outweigh the risks.

Note the papers on the effects of including DHA and ARA in the parenteral emulsions needed by seriously ill patients. In infants with severe liver disease and short bowel syndrome, these PUFAs reversed the disease significantly more quickly and more often compared with standard soybean oil emulsion. In the U.S., these formulas are approved only under compassionate protocols. What is needed to change the regulations so that severely ill patients receive essential nutrients?
Every 2 years the International Society for the Study of Fatty Acids and Lipids (ISSFAL) convenes to discuss advances in the field through plenary sessions, oral presentations and posters. This year’s May meeting in Kansas City, USA, also included a satellite workshop on conducting clinical trials.

Some highlights from the meeting include:

- The Alex Leaf Award Lecture by Art Spector, in which Spector discussed the epoxygenase derivatives of cytochrome p450 enzymes known as “EETs” (epoxyeicosatrienoic acids). These are formed in endothelial cells from arachidonic acid and become incorporated into cell membrane phospholipids where they have anti-inflammatory, vasodilation, fibrinolytic and angiogenic properties; they become active after a myocardial infarction to protect the heart.

- The underlying mechanisms involved in fighting inflammation entail distinct anti-inflammatory activities and pro-resolving ones. Lipoxins, resolvins and protectins derived from long-chain polyunsaturated fatty acids (LC-PUFAs) contribute to reduced production of inflammatory mediators and the recruitment and activity of immune cells. In addition, these substances have specific pro-resolving actions, such as blocking neutrophil entry into inflamed sites and altering proteins in the cytoskeleton that arrests cell activity. The multi-level actions of these substances together have highly potent resolving actions in disease models of periodontitis, lung, eye, gastrointestinal, kidney and skin pathologies and underscore the contributions of omega-3 LC-PUFAs in the resolution phase of inflammation.

- Investigation into the mechanisms of action for lithium, valproic acid and carbamazepine—drugs used to stabilize mood in bipolar mania—suggest that these agents modify neuroreceptor-mediated arachidonic acid signaling, which is over-active in this condition and others, such as Alzheimer’s disease and brain inflammation. Studies suggest that supplementation with n-3 LC-PUFAs would also counteract the arachidonic acid cascade.

- Higher maternal intake of n-3 LC-PUFAs in pregnancy was associated with lower childhood adiposity at age 3, suggesting that western diets low in n-3 LC-PUFAs favor the development of adiposity later in life.

- Supplementation of post-menopausal women with ethyl-EPA for 8 weeks was associated with a significant 55% decrease in the frequency of hot flashes compared with women consuming a placebo, but the intensity of the hot flashes was unaffected. Supplementation of a similar group of women experiencing post-menopausal psychological distress with both EPA (1.0 g/day) and DHA (150 mg/day) was without effect on psychological distress, but in women with major depression, n-3 LC-PUFA supplementation was associated with a significant improvement in psychological distress and depression compared with the placebo.

- The effect of PUFAs on bone mineral density has attracted attention because of the loss of bone mass in the elderly and the importance of accruing bone mass during growth. A study of the relationship between bone mineral density and serum phospholipid n-6 PUFAs in 8-year old children reported that linoleic acid was inversely associated with bone density in the total body, lumbar spine and hip, but that ARA was positively associated with bone density in the total body and hip. Omega-3 PUFAs were unrelated to bone density.
Two independent posters described evidence that n-3 LC-PUFA concentrations increase with age. In one report, supplementation with n-3 LC-PUFAs resulted in lower concentrations of free fatty acids, with a greater reduction in fatty acids in young adults compared with elderly participants. DHA supplementation did not raise free DHA concentrations in the plasma of older adults. In a different study on aging, the Maastricht Aging Study reported an inverse association between plasma phospholipid DHA concentration and cognitive speed after 12 years, but not with cognitive performance in healthy individuals. However, higher fish consumption was linked to better memory. Something’s amiss!

The likelihood of developing advanced age-related macular degeneration was significantly lower in people with the highest intake of DHA. Risk was further reduced in people who consumed aspirin more than 5 times/week and had high DHA intakes.

Behavior and learning disorders in children cover a spectrum with overlapping symptoms and distinct subsets of characteristics. In children with attention deficit with or without hyperactivity (ADHD), inattention may be the greatest impairment. In a randomized, placebo-controlled trial, a large subgroup of children with inattention experienced a 47% reduction in ADHD symptoms after 6 months’ supplementation with n-3 LC-PUFAs containing a small amount of γ-linolenic acid. Another controlled trial in ADHD children using only EPA reported significant treatment benefits related to the predominant behavioral subtype, not in the overall sample. Responses were the greatest in children with the lowest EPA concentrations at baseline.

Chronic alcoholism depletes DHA in the orbitofrontal cortex of the brain and reduces DHA incorporation and turnover. These changes are thought to impair neurotransmission.
Remnant-Like Particles Fall in Men with High Triglycerides Taking DHA Supplements

Patients with a specific pattern of plasma lipoproteins, sometimes described as atherogenic dyslipidemia, have 3 times the risk of atherosclerosis compared with patients not having such a lipid pattern. This risky profile includes small dense low-density lipoproteins, elevated triglycerides and low concentrations of high-density lipoproteins. A class of particles formed from the breakdown of triglyceride-containing lipoproteins called remnant-like particles are also believed to be highly atherogenic and can be incorporated into developing atherosclerotic plaque without prior oxidation. They are abundant in patients with metabolic syndrome and type 2 diabetes. Patients with these risky lipid profiles usually have low concentrations of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs), as reflected in the omega-3 index or the ratio of eicosapentaenoic acid (EPA) to arachidonic acid (ARA).

Fish oil or EPA significantly reduces remnant-like lipoprotein particles, which are highly atherogenic. The effect of DHA on these particles has not been reported.

The consumption of fish oil or EPA and DHA combined has been associated with significant reductions in triglycerides and remnant-like particles. EPA alone was linked to lower remnant-like particles in patients with metabolic syndrome or type 2 diabetes, and was associated with reduced triglycerides in mildly hyperlipidemic men. DHA alone or in combination with EPA had similar effects in reducing triglycerides in patients with elevated triglycerides and coronary artery disease. Until now, however, the effect of DHA alone on remnant-like particles had not been reported.

In this study, Darshan Kelley and colleagues at the U.S. Department of Agriculture’s Western Human Nutrition Research Center in California, USA, recruited 34 men with serum triglycerides of 1.7 to 4.5 mmol/L (150 to 400 mg/dL) for a randomized, placebo-controlled, double-blind trial using supplements of DHA or an olive oil placebo for 90 days. Following an 8-day baseline period, patients were randomized to consume 3.0 g DHA/day in 7.5 g oil or 7.5 g olive oil/day for 90 days. This dose is midway between the American Heart Association’s recommended dose of 2 to 4 g n-3 LC-PUFAs/day for reducing triglycerides. Data were available for 14 participants in each group.

At baseline, those in the DHA group had significantly higher plasma linoleic acid and lower total monounsaturated fatty acids compared with the placebo group. Consumption of DHA significantly increased plasma DHA (255%) and EPA (81%) at 45 and 90 days compared with baseline values. It also significantly reduced ARA (24%) and total n-6 PUFA concentrations (7%). A similar pattern of changes was observed in the red blood cell fatty acids, although the DHA increase was smaller at both 45 and 90 days (179%) and the increase in EPA greater (120%). As with plasma lipids, total red cell n-6 PUFAs declined further between days 45 and 90. There were no significant changes in the plasma or red blood cell lipids in the placebo group.

Remnant lipoprotein cholesterol concentrations were significantly reduced in the DHA group after 45 (-36%) and 90 days (-21%) of supplementation, but were unchanged in the placebo group. Interestingly, the remnant cholesterol concentration increased between days 45 and 90 in the DHA treatment group, but remained significantly lower than baseline values at the end of the study. The reduction in remnant cholesterol was strongly and significantly correlated with changes in triglycerides, reduced oleic acid levels and less strongly with the ratio of total cholesterol to high-density lipoprotein cholesterol and apolipoprotein B. The association between remnant cholesterol and oleic acid was unexpected and DHA consumption was marginally associated with lower plasma oleic acid concentrations ($P=0.06$).

These findings with DHA supplementation are consistent with those reported for EPA supplementation and remnant cholesterol in diabetic and metabolic syndrome patients. In the EPA and diabetes study, the consumption of 900 mg to 1.8 g EPA/day for three months was accompanied by a 77% reduction in remnant cholesterol. In another study, patients with metabolic syndrome who consumed 1.8 g of EPA/day for three months experienced significantly reduced remnant triglycerides, but not cholesterol concentrations. Reductions in remnant cholesterol would be considered beneficial and their fatty acid composition may be important as well. It was reported that macrophages incorporated remnant particles incubated with palm or olive oils more rapidly than those incubated with corn or fish oil, but greater lipid accumulation occurred only with the saturated fatty acid-rich particles. Thus, reducing the amount of remnant-like particles and increasing their n-3 LC-PUFA composition may reduce the formation of macrophage foam cells, the precursor of atherosclerotic plaque.
As expected, the ratio of EPA to ARA and the omega-3 index (% EPA+DHA in red blood cells as % of the total fatty acids) were significantly increased at days 45 and further at 90 days in those consuming the DHA supplements, but not in the placebo group. Both indices are strongly predictive of the risk of sudden death and cardiovascular risk. Findings from this study add to the evidence of lower risk of cardiovascular disease, particularly in patients at increased risk of the disease, with the consumption of n-3 LC-PUFAs or DHA supplementation.


### MATERNAL & INFANT HEALTH

**Extra DHA and ARA in Preterm Infants Fed Human Milk Boosts Cognition**

Infants born weighing less than 1,500 g face greatly increased chances of morbidity and mortality, impaired neurodevelopment and behavioral problems. They also miss out on the LC-PUFAs they would have obtained in utero. Is the amount in breast milk enough to meet their needs?

The increased health risks for infants born before 37 weeks' gestation are well known, but infants born weighing less than 1,500 g face even greater morbidity and increased risk of mortality, impaired neurodevelopment and behavioral problems. Many of these risks relate to inadequate nutrient supply and the lack of nutrient and fat reserves. In particular, these very low birthweight infants are deprived of the long-chain polyunsaturated fatty acids (LC-PUFAs) they would have received from the mother in the last trimester. Thus, it is imperative that preterm infants receive fluids containing these fatty acids, but what is the optimum dose? Most preterm formulas contain LC-PUFAs in the lower half of the range reported in breast milk—0.2% to 0.35% of total fatty acids.

Christine Henriksen and colleagues at the University of Oslo, Norway, noted that breast milk LC-PUFA concentrations are considerably below what these infants would obtain had they remained in utero. It is estimated that for docosahexaenoic acid (DHA), an omega-3 (n-3) LC-PUFA, the uterine accretion rate is about 50 mg/day, whereas a full enteral intake of supplemented formula or breast milk would provide between 13 and 26 mg/day. These investigators explored whether giving higher levels of arachidonic acid (ARA) and DHA than what are usually found in human milk would have any effect on the cognitive outcomes of very low birthweight infants at 6 months of age, corrected for gestational age.

The investigators used a parent-completed global assessment of mental and motor development, the Ages and Stages Questionnaire. In addition, they assessed event-related potentials (ERPs), which measure brain activity from standard electrode recordings. These provide information about changes linked to physical or cognitive events. The amplitude in the negative central component of these charts is larger for new, presumably interesting, stimuli and decreases as a stimulus is repeated. The tests used a standard image 70% of the time, showing novel images only once and not in succession for 30% of the presentations. The novel images elicit a negative, larger, long-lasting ERP compared with the standard image. The investigators hypothesized that the intervention group would show a more marked decrease of the negative amplitude with repetition of the standard image compared with the control group, but no difference between groups for the new image.

All infants received human milk from birth and, as the feeding increased, the milk was fortified with proteins, minerals, vitamins, iron and folic acid. Once the infants were receiving more than 100 mL of human milk/kg body weight per day, the human milk was supplemented with either the treatment or control oil at 0.5 mL/100 mL of milk. The treatment oil contained 31 mg of ARA and 32 mg of DHA/100 mL and the control oil contained 16 mg alpha-linolenic acid and 127 mg linoleic acid/100 mL dispersed in soybean medium-chain triglyceride oil. All infants received some LC-PUFAs from breast milk, 17 and 26 mg/100 mL of ARA and DHA, respectively. Supplementation continued until the infant was discharged or the 100 mL bottle of study oil was depleted, on average 63 days. Infants not breastfeeding at discharge changed to term formula containing LC-PUFAs.

The original cohort included 222 consecutively born very low birthweight infants of whom 141 were eligible for the study. Twelve infants in each group were excluded, leaving 129 infants who completed the intervention, 62 and 67 in the intervention and control groups, respectively. Participating infants had an average gestational age of 28 weeks and birthweight of 1,090 g. Two control infants died during the course of the study, one from congenital malformations not originally detected and the other from respiratory failure. Energy and nutrient intakes did not differ between the groups during the study except for DHA and ARA consumption. DHA intakes were 59 and 32 mg/kg/day for the intervention and control groups, respectively, and for
ARA were 47 and 22 mg/kg/day in each group. There were no significant differences between the groups in growth, length gain and increased head circumference during the study.

Plasma fatty acid patterns generally reflected the diet, with an increase of 12% DHA in the intervention group and a decrease of 9% in the control group. Arachidonic acid concentrations decreased in both groups, by 6% in the supplemented group and 24% in the control infants.

Assessment at 6 months with the Ages and Stages Questionnaire revealed a significant advantage in problem-solving for the supplemented infants compared with the controls (Table). Total scores were higher, but not significantly so. Scores in the other domains of this assessment did not differ significantly. In the ERP assessments, 98 recordings were made, but 17 were discarded because of impaired vision (2), infant crying (7) or technical failure (8). In the available recordings, supplemented infants had significantly lower amplitudes compared with control infants (P=0.01) as hypothesized. There were no group differences in response to the novel images. These data were interpreted to signify a beneficial effect on recognition memory in the LC-PUFA-supplemented infants.

Table. Cognitive outcome measures in very low birthweight infants at 6 months of age assessed by the Ages and Stages Questionnaire and ERPs*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention group Mean ± SD</th>
<th>Control group Mean ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages &amp; Stages Questionnaire Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total score</td>
<td>221 ± 32</td>
<td>215 ± 39</td>
<td>NS</td>
</tr>
<tr>
<td>Communication</td>
<td>45.4 ± 7.9</td>
<td>46.6 ± 9.1</td>
<td>NS</td>
</tr>
<tr>
<td>Gross motor</td>
<td>33.3 ± 11.5</td>
<td>30.9 ± 11.1</td>
<td>NS</td>
</tr>
<tr>
<td>Fine motor</td>
<td>45.2 ± 10.7</td>
<td>45.8 ± 14.3</td>
<td></td>
</tr>
<tr>
<td>Problem-solving</td>
<td>53.4 ± 7.0</td>
<td>49.5 ± 9.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Personal-social</td>
<td>43.2 ± 12.8</td>
<td>42.2 ± 12.3</td>
<td>NS</td>
</tr>
<tr>
<td>ERPs (μV) at 6 mo.</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard image</td>
<td>-8.9 ± 7.8</td>
<td>-13.2 ± 7.2</td>
<td>0.01</td>
</tr>
<tr>
<td>Novel image</td>
<td>-17.4 ± 9.6</td>
<td>-19.5 ± 11.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Event-related potentials measured in micovolts

This study presents evidence that providing very low birthweight infants a higher dose of DHA and ARA than is found in breast milk, an amount akin to what the infant would receive in utero, benefits infant cognition without adversely affecting growth.


High Prenatal DHA Fosters Better Visual, Cognitive and Motor Development

It is becoming more evident that a mother’s nutritional status during pregnancy, especially with regard to long-chain polyunsaturated fatty acids (LC-PUFAs) is critically important to her infant’s developmental outcomes, perhaps more so than the infant’s nutrition after birth. Postnatal nutrition is, of course, important for child development, especially for infants born preterm, but the apparent long-lasting effects of maternal nutrition have been underappreciated. There is greater accretion of LC-PUFAs during fetal development than after birth and several, although not all, studies have reported significant associations between perinatal LC-PUFA status and cognitive function, attention and behavior.

A longitudinal study of 109 Inuit mothers and their infants, begun in 1995, is the basis for this report on pregnancy outcomes and various developmental effects associated with maternal LC-PUFA status. Participants in the study were recruited from three Hudson Bay villages in Nunavik, northern Quebec, Canada. Cord blood samples from 109 infants, maternal blood obtained at delivery from 91 mothers and...
1-month postnatal maternal milk samples from 67 mothers were available for analysis of fatty acids, heavy metals and polychlorinated biphenyls (PCBs). The investigators assessed infant visual acuity and novelty preference at 6 months with the Teller acuity cards and Fagan Test-II of infant intelligence, respectively. At 11 months of age, the infants were assessed with the Teller and Fagan tests again and with the Bayley Scales of Infant Development-II for cognitive and motor development. Greater gestational age and birthweight compared with southern Quebec newborns have been previously reported for this study.

Cord docosahexaenoic acid (DHA) concentration in plasma phospholipids as a percent of total fatty acids (3.7%) was significantly higher than in maternal plasma (2.8%) and three times higher than levels reported for southern Quebec (Table 1). On the other hand, arachidonic acid (ARA) was two times lower in the same comparison. In maternal milk, DHA and ARA were 0.6 and 0.3% of total fatty acids, respectively. This DHA value is twice as high as the mean (0.3%) recently reported for worldwide samples of breast milk, but ARA was about two-thirds of the worldwide mean (0.5%). It is likely that the high intakes of DHA suppressed ARA concentrations, as has been frequently observed. Maternal and cord plasma DHA were strongly correlated (r=0.6, P<0.01), but ARA was not (r=0.15). These relationships support the suggestion that the fetus is highly dependent upon the mother for DHA, but less so for ARA. The latter may be more abundant in maternal diets than DHA or may be more readily mobilized from stores to meet fetal demands.

For infant developmental outcomes, better visual acuity at 6 months was significantly related to the ratio of DHA/ARA in cord plasma, but was not related to DHA levels at either 6 or 11 months (Table 2). However, increased visual acuity was observed in the quartile of infants with the highest cord DHA concentrations. The Fagan test of novelty preference was significantly associated with DHA in a dose-dependent manner at 6 months, but not at 11 months. This finding was considered important because 6-month novelty preference is predictive of childhood IQ. Similarly, the Bayley Scales of Mental and Psychomotor Development were significantly related to cord DHA at 11 months and scores were generally dose-related. Cord DHA concentration was unrelated to any measure of postnatal growth.

Postnatal DHA intake was associated with slower weight gain through 11 months, a finding that has been reported previously, but thought to be of questionable biological significance. Breast-feeding has also been associated with slower weight gain and lower body mass index at 1 year of age compared with not breast-feeding. In this study, postnatal DHA intake from breast-feeding, taking into account breast milk DHA and length of exclusive breast-feeding, was not related to infant cognitive and motor development, as reflected in the Bayley Scales at 11 months of age. In these communities, 88% of infants were exclusively breast-fed for at least one month and 56% for at least three months. These findings contrast with studies on LC-PUFA-supplemented infant formulas in which prenatal DHA supply may have been appreciably lower than in this population.

An important aspect of this report is its ability to analyze the relationship of varying prenatal exposure to DHA, including relatively high levels, to diverse infant outcomes at different times. Most western diets provide only low levels of DHA prenatally, unless n-3 LC-PUFA supplements are consumed. In spite of this population’s exposure to various environmental contaminants, several of which were controlled in the analysis (PCBs, mercury, lead), prenatal DHA was associated with greater birthweight, gestational age

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Cord plasma phospholipids % total fatty acids*</th>
<th>Maternal plasma phospholipids</th>
<th>Maternal milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>DHA</td>
<td>3.7 ± 1.1</td>
<td>2.8 ± 1.6</td>
<td>0.6 ± 0.6</td>
</tr>
<tr>
<td>ARA</td>
<td>9.3 ± 1.7</td>
<td>4.0 ± 1.4</td>
<td>0.3 ± 0.1</td>
</tr>
<tr>
<td>DHA/ARA</td>
<td>0.4 ± 0.1</td>
<td>0.7 ± 0.1</td>
<td>1.7 ± 1.5</td>
</tr>
</tbody>
</table>

* Mean ± SD

Table 2. Standardized regression coefficients for the relationship between prenatal DHA and developmental outcomes

<table>
<thead>
<tr>
<th>Outcome measure</th>
<th>n</th>
<th>Standardized regression coefficient β*</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visual acuity, 6 mo</td>
<td>78</td>
<td>0.17</td>
<td>NS</td>
</tr>
<tr>
<td>Visual acuity, 11 mo</td>
<td>80</td>
<td>-0.1</td>
<td>NS</td>
</tr>
<tr>
<td>Fagan novelty preference, 6 mo</td>
<td>76</td>
<td>0.3</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Fagan novelty preference, 11 mo</td>
<td>84</td>
<td>0.0</td>
<td>NS</td>
</tr>
<tr>
<td>Bayley Scales-II mental, 11 mo</td>
<td>80</td>
<td>0.23</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Bayley Scales-II psychomotor, 11 mo</td>
<td>80</td>
<td>0.18</td>
<td>NS</td>
</tr>
</tbody>
</table>

*2-tier multiple regression analysis with DHA and then control variables entered individually and retained if the standardized regression coefficient was altered by at least 10%.
Prenatal DHA was associated with greater birthweight, gestational age, Fagan novelty preference and visual acuity at 6 months of age, and Bayley Scores for mental and psychomotor development at 11 months of age. These results were observed in spite of maternal exposure to several environmental contaminants.

Observations with visual acuity and the Fagan tests at 11 months of age, but these did not reach statistical significance. While exposure to high levels of environmental contaminants is clearly undesirable, these results support those from the U.K., where children of mothers with the highest fish consumption and mercury exposure were the least likely to have suboptimal neurodevelopmental outcomes.


Adverse Fatty Acid Profiles in Early Pregnancy Linked to Smaller Infants

Minimizing the chances of preterm delivery, low birthweight and being born small-for-gestational-age favor healthier child outcomes. Long-chain polyunsaturated fatty acids (LC-PUFAs) from both the omega-3 (n-3) and omega-6 families (n-6) are essential for fetal growth and development. Recent reviews of randomized controlled studies on maternal supplementation with n-3 LC-PUFAs favor longer gestation and greater head circumference, but supplementation had little effect on preterm delivery, rate of low birthweight or infant growth. These findings do not negate the beneficial effects of maternal n-3 LC-PUFA supplementation or higher DHA status in pregnancy on infant neurodevelopmental outcomes, visual acuity and behavior that have been reported. Nonetheless, at least one study reported an association between greater n-3 LC-PUFA intake from fish and reduced fetal growth, while another reported that fish consumption reduces the chance of having a small for gestational age infant. Risk of delivering a small-for-gestational-age infant also increases with maternal smoking, hypertension, low pre-pregnancy body mass index and low maternal weight gain.

Van Eijssen and colleagues at the Amsterdam Municipal Health Service and the Universities of Amsterdam and Maastricht sought to distinguish between the effects of prolonged gestation and maternal fatty acid status in early pregnancy on fetal outcomes. The investigators did so by specifying at the outset the cofactors of interest and examining their association with maternal fatty acid status at the mothers’ first prenatal visit—about 12 weeks’ gestation. The study emphasized all LC-PUFAs and their 18-carbon precursors, and elaidic acid (18:1n-9t), an industrially produced trans fatty acid. Pregnant women were recruited from participating hospitals in Amsterdam. Of the 12,373 women invited to participate, 8,266 responded and 4,389 women participated. After the exclusion of women with diabetes, hypertension or preterm delivery, fatty acid profiles were obtained from 3,704 mothers who gave birth to live singleton infants. Primary outcomes were birthweight, small-for-gestational-age (birthweight below the 10th percentile for gestational age based on Dutch standards) and plasma phospholipid fatty acids. Other sociodemographic variables and lifestyle factors were obtained by a questionnaire at enrolment.

Birthweight was positively associated with all n-3 PUFAs and dihomo-γ-linolenic acid (n-6), the elongation product of γ-linolenic acid, and negatively with all other n-6 PUFAs and elaidic acid in univariate analysis. When the analyses were adjusted for physiologic and sociodemographic factors, the highest concentrations of eicosapentaenoic acid (EPA, an n-3 LC-PUFA) and dihomo-γ-linolenic acid remained significantly associated with birthweight, while the highest fatty acid concentration of arachidonic acid (ARA) was associated with low birthweight. A similar pattern for the chance of giving birth to a small-for-gestational-age infant was observed for women with the lowest levels of n-3 eicosatetraenoic and docosapentaenoic acids and for the 2 lowest quintiles of dihomo-γ-linolenic acid. Adjustment for multiple cofactors removed the significant adverse association with elaidic acid.

The investigators also devised a fatty acid score (“cumulative exposure score”) based on the fatty acids significantly associated with birthweight in univariate analysis. The highest score, ≥6, signified the most adverse fatty acid profile. A multivariate analysis of these scores women with scores of ≥4 had infants weighing an average of 72 g less and were

Long-chain PUFAs prolong gestation slightly and are required for optimal pregnancy outcomes. Whether these fatty acids directly affect fetal growth is uncertain and data are limited and conflicting. Screening women early in pregnancy may suggest whether they have increased risks because of their LC-PUFA status.
1.5 times more likely to have small-for-gestational-age infants compared with mothers having the lowest or most favorable score (Table). Infants of mothers with the most adverse scores of 6 or more (7% of the sample) were 125 g lighter and were twice as likely to be small-for-gestational-age.

Table. Multivariate associations between maternal fatty acid score and birthweight and small-for-gestational-age outcomes

<table>
<thead>
<tr>
<th>Fatty acid exposure score*</th>
<th>n</th>
<th>Birthweight</th>
<th>Small for gestational age %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-1</td>
<td>1716</td>
<td>3,569 ± 487</td>
<td>9.4</td>
</tr>
<tr>
<td>2-3</td>
<td>1192</td>
<td>3,510 ± 463</td>
<td>10.0</td>
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<tr>
<td>4-5</td>
<td>519</td>
<td>3,408 ± 497</td>
<td>16.4</td>
</tr>
<tr>
<td>≥6</td>
<td>277</td>
<td>3,329 ± 469</td>
<td>23.8</td>
</tr>
</tbody>
</table>

* Higher scores indicate a more adverse fatty acid profile

Few studies have examined the relationship between maternal fatty acid status in early pregnancy and birth outcomes, although the available data suggest that low n-3 LC-PUFA status assessed in cord blood is associated with poorer infant outcomes. In this report, both n-3 and n-6 fatty acids were related to birthweight, with low concentrations of most n-3 LC-PUFAs, but high concentrations of ARA being negatively associated with birthweight and greater risk of small-for-gestational-age infants. Higher levels of the precursor of ARA were associated with positive outcomes, an association that may be related to insulin activity or the competition between ARA and dihomo-γ-linolenic acid.

Mothers with higher concentrations of most n-3 LC-PUFAs and lower levels of ARA were significantly less likely to have lower birthweight infants or those who were small for their gestational age. Industrially produced trans fatty acid was not associated with either outcome in multivariate analysis.

The findings reported here are consistent with the effects of n-3 LC-PUFA supplementation later in pregnancy on prolonged gestation. They are consistent with similar results for pregnancy outcomes in women with low fish consumption. As the authors note, a mother’s fatty acid profile in early pregnancy predicts her profile in late pregnancy and may influence the growth and development pattern of the fetus. This report suggests that paying attention to the concentrations of γ-linolenic and EPA in early pregnancy may be important for achieving desirable concentrations of n-3 and n-6 PUFAs without increasing ARA unduly.

High Fish Consumption Linked to Better Child Test Scores, Mercury Clouds Results

A new report from an ongoing study of maternal fish consumption and child development in the U.S. notes that higher fish consumption was associated with better child cognition in one test. Higher maternal mercury exposure in a small portion of the sample was linked to poorer test scores, but not when both fish and mercury were considered.

Recommendations to increase the consumption of long-chain omega-3 fatty acids (n-3 LC-PUFAs) for their many health benefits frequently suggest two meals of fish/week. In some countries, this advice has been viewed skeptically due to fears of environmental contaminants in fish. Of the various contaminants that may occur in fish, methylmercury is of greatest concern to pregnant and nursing women. This is because of its potentially neurotoxic effects on the fetus and young infant. One study reported a decline in fish consumption following a mercury advisory targeted to pregnant and nursing women. Regular scare campaigns by activist groups concerned mainly about environmental issues and fisheries remind consumers of the potential hazards associated with contaminants. On the other hand, frequent news stories about the health benefits of eating seafood remind the public of the benefits of fish consumption, considered by experts to outweigh the potential risks.

Because the developing fetus and young infant are at greatest risk from the potential neurotoxicity of methylmercury that comes mainly from fish consumption, much attention has focused on the neurodevelopmental outcomes of the offspring of mothers who consume fish regularly. The longitudinal study of mothers and infants in the Faroe Islands has reported neurobehavioral deficits in the children of mothers exposed to methylmercury through the consumption mainly of pilot whale. These deficits were observed when the children were 7 and 14 years of age and may have been exacerbated by co-exposure to polychlorinated biphenyls. On the other hand, in the absence of pilot whale mercury, the effects of fish consumption were all positive. In contrast to the Faroe Islands studies, those conducted in the Seychelles Islands, where fish consumption averages 12 meals/wk, have reported no significant associations between prenatal methylmercury exposure and child developmental outcomes.
The common ground between these two longitudinal studies is that when methylmercury and fish consumption are examined, fish consumption is without adverse effects on developmental outcomes in both populations—in fact, it is beneficial. It is the high exposure to methylmercury from eating pilot whale in the Faroe Islands that accounts for the main differences between the two studies.

Other data from different populations consuming large amounts of fish, often with high levels of contaminants, indicate that the net benefits of maternal fish consumption on childhood development are positive (see preceding article). That is not to say that fish contaminants have no effect, but that the net outcome, partly from the n-3 LC-PUFAs in seafood, is beneficial to child development. Additional data from a longitudinal study in Massachusetts, USA, described here are consistent with these earlier reports.

In Project Viva, 341 mothers who gave birth to a single infant provided information about their diet and fish intake during the second trimester and provided a blood sample. Of these mothers, 98 also gave a hair sample for mercury analysis. Information about the frequency and types of fish consumed were obtained and frequency was combined into three categories: never or < once/mo, two or fewer servings/wk and more than two servings/wk. Cognitive outcomes in children at 3 years of age were assessed using the Peabody Picture Vocabulary Test (PPVT) and the Wide Range Assessment of Visual Motor Abilities (WRAVMA), which evaluates 3 domains of visual motor development: visual-spatial (matching test), visual-motor (drawing test) and fine-motor skills (pegboard test). The PPVT test measures an individual’s receptive (hearing) vocabulary for standard American English. It provides a quick estimate of verbal ability or scholastic aptitude. Because it can be used for all ages above 2.5 years, it was administered to the children and their mothers.

On average, mothers consumed 1.5 fish meals/wk, with 40 (12%) consuming more than two fish meals and 47 (14%) never eating fish. The study observed a significant correlation between red blood cell mercury content and fish intake, as has been frequently reported. However, even in women reporting never eating fish, the mean mercury level was nearly half that of women who ate two or fewer servings/wk (1.9 vs 3.9 ng/g) and a third the level observed in the highest fish consumption group (1.9 vs 5.6 ng/g). Assuming the validity of this observation in 47 mothers, this finding suggests that non-fish sources of mercury contribute appreciably to total mercury exposure. Hair mercury was highly correlated with red blood cell mercury and fish consumption.

After adjusting for parent and child characteristics, maternal fish intake of more than two servings/wk compared with not eating fish was associated with significantly higher child visual motor ability scores for total scores and for the drawing component of the evaluation. Adjustment for mercury intake strengthened these associations. There were no significant associations between maternal fish consumption with PPVT test scores. Further, there was no apparent advantage of fish consumption below two servings/wk compared with not eating fish. A similar observation was reported in a large study of behavioral outcomes and maternal fish consumption in the U.K., where only fish consumption above two 6-oz servings/wk was of significant benefit.

In subgroup analysis, children whose mothers who consumed canned tuna at least twice/wk (n=28) had children with significantly higher PPVT scores compared with mothers who never ate canned tuna (n=130).

Higher maternal red cell mercury levels were associated with poorer child performance on the PPVT test and the WRAVMA tests for matching and total scores in adjusted analysis. Including maternal fish consumption in the analysis strengthened these associations. When maternal fish and mercury levels were analyzed together for combined effects on the WRAVMA scores, higher fish consumption was associated with significantly better scores compared with lower fish intake. The effect of high mercury level was to reduce the effect of fish consumption, but these effects did not reach statistical significance. The net effect still favored higher scores with the most frequent fish consumption (Table).

### Table. Associations of visual motor scores in children aged 3 according to prenatal maternal fish consumption and red blood cell mercury levels

<table>
<thead>
<tr>
<th>Frequency of fish consumption</th>
<th>Mercury ≤90th percentile WRAVMA* total score (95% CI)</th>
<th>Mercury top decile WRAVMA total score (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 2 serv/wk</td>
<td>31</td>
<td>5.9 (1.0 to 10.9)</td>
</tr>
<tr>
<td>≤ 2 serv/wk</td>
<td>229</td>
<td>1.8 (–1.8 to 5.3)</td>
</tr>
<tr>
<td>Never</td>
<td>47</td>
<td>0 (Referent)</td>
</tr>
</tbody>
</table>

*Wide Range Assessment of Visual Motor Abilities, adjusted for multiple confounding variables
Maternal fish intake of more than 2 servings/wk compared with not eating any fish was associated with significantly higher child visual motor ability scores. High maternal mercury levels were associated with poorer test results, but the number of samples was very small and only partly associated with fish intake.

Several points about this paper are worth noting. One is that the number of mothers consuming fish never or more than twice/wk was small, 47 and 40, respectively. In the combined analysis of red cell mercury and fish consumption, especially in the top decile of mercury, the numbers are even smaller. This means conclusions should be drawn with caution. Another is the fact that only 23% of mothers who consumed fish more than twice a week were likely to have the highest concentrations of red cell mercury. There are several interpretations of this observation. One is that these women were likely to consume fish low in mercury. Another possibility is that red cell mercury could accumulate from other sources of exposure than eating fish. Finally, the WRAVMA and PPVT are less widely used assessments of childhood visual and cognitive function, but may be more suitable for 3-year olds than the Bayley Scales of Infant Development.

The authors suggest that no lower threshold exists for the adverse effects of prenatal mercury exposure, but reported no significant effects when both mercury and fish consumption were taken into account (Table). This is an important issue and is the main reason why women of childbearing age are concerned about consuming fish, especially during pregnancy and lactation. The neurotoxicity of methylmercury is well known at high levels of exposure, but has not been convincingly demonstrated in populations exposed to fish and methylmercury at levels well above those reported in this study. There is no question that women of childbearing age should be encouraged to consume low-mercury fish, but as this study makes clear, the net effect of higher rather than lower fish consumption is better childhood neurodevelopmental outcomes.


Atopic Dermatitis

High Dose DHA Improves Eczema Symptoms and Reduces IgE Production by PBMC

Atopic dermatitis, sometimes called atopic eczema, is one of the three most common manifestations of allergic disease. About 10% to 20% of people worldwide develop the condition, according to the American Academy of Dermatology, and its prevalence in adults shows wide geographic variation. Eczema usually appears before the age of 5 with dry, inflamed, itchy skin and increased immunoglobulin E (IgE) responses. Atopic eczema is more common in children with a parent who has the condition and the majority of cases subside in adolescence.

Although the involvement of n-3 LC-PUFAs in the onset and severity of eczema has been reported, dietary treatment of eczema with n-3 LC-PUFAs has not been investigated. In this study, high-dose DHA was evaluated in adults with the condition.

Polyunsaturated fatty acids (PUFAs) appear to be involved in the development and severity of atopic diseases, but how is unclear. Increasing occurrence of atopic eczema has been linked to western diets with low intake of omega-3 polyunsaturated fatty acids (n-3 PUFAs). Breast milk high in saturated fatty acids and low in n-3 PUFAs was associated with the occurrence of atopic dermatitis in children in the first year of life. One study reported that total n-3 PUFAs and two long-chain (LC) n-3 PUFAs were higher in the breast milk consumed by children who were sensitized to food and air-borne allergens at 6 and 24 months of age compared with those not sensitized. Others have reported that maternal breast milk fatty acids were not associated with atopic eczema in high-risk infants at 6 weeks or 6 months, but higher concentrations of n-6 PUFAs were associated with non-atopic eczema.

Concentrations of linoleic acid may be elevated in atopic eczema, suggesting a possible reduction in the desaturation of this fatty acid to gamma-linolenic acid. Interestingly, children who wore undershirts coated with borage oil, which contains 20% to 23% of gamma-linolenic acid, had significantly reduced symptoms after two weeks compared with children who wore untreated shirts. A meta-analysis of 26 clinical studies on evening primrose oil concluded that this oil, also rich in gamma-linolenic acid (8% to 10%), has beneficial effects in atopic eczema. Maternal supplementation with n-3 LC-PUFAs during pregnancy was associated with less severe atopic eczema symptoms in the offspring, but not in the incidence of the condition.
Few studies have examined the treatment of atopic eczema with n-3 PUFAs. In one report of hospitalized patients with severe atopic dermatitis who were infused with either n-3 LC-PUFAs or n-6 PUFAs for 10 days, those receiving n-3 LC-PUFAs had markedly greater improvement in their symptoms compared with those given n-6 PUFAs. A review of controlled trials using essential fatty acids concluded that these fatty acids were not clinically relevant to the severity of atopic dermatitis. Others have reached similar conclusions. However, a small open label trial reported promising results.

To find out whether high doses of n-3 LC-PUFAs might be effective, Christof Koch and colleagues at Charité-Universitätsmedizin in Berlin studied 53 adults with atopic eczema aged 18 to 40 years. Participants were stratified by sex, age and body mass index and randomized to consume a high dose of DHA, 5.4 g/day, or an isocaloric placebo of short-chain saturated fatty acids for 8 weeks. Patients continued with their usual medications. The severity of their eczema was evaluated by the same dermatologist at baseline and 8 weeks, using the severity scoring of atopic dermatitis (SCORAD) index. Forty-four patients completed the study.

After 8 weeks, supplementation with DHA resulted in significantly increased DHA, eicosapentaenoic acid (EPA) and n-3 docosapentaenoic acid concentrations in plasma and a significant decrease in arachidonic (ARA), alphalinolenic and oleic acids. Eczema severity declined in both groups, but the improvement was significant only in the DHA-treated group (median decrease in SCORAD -18% vs -11% in DHA and control groups, respectively). Improvement in eczema symptoms appeared at the end of 4 weeks. Better scores in the DHA group resulted mainly from a reduction in the affected areas from a median of 12 to 7. However, at the end of 8 weeks, there was no significant difference in the clinical scores between the 2 groups, probably because of a placebo effect.

The investigators also measured immunoglobulin E (IgE) production in anti-CD40/IL-4-stimulated peripheral blood mononuclear cells (PBMC) and observed a significant decrease in production only in the cells from DHA-treated patients. However, total IgE in the sera of both groups was unaltered.

This clinical trial indicates that further exploration of the treatment of atopic dermatitis with n-3 LC-PUFAs is warranted. Whether such a high dose of DHA is necessary or effective remains to be established. Neither is it clear that only DHA is effective. Given the benefits of gram quantities of fish oil in several inflammatory conditions, such as rheumatoid arthritis, the effectiveness of either EPA or DHA or both deserves clarification. These findings may ensure that these questions find answers.


Atopic Dermatitis Severity and Skin Barrier Function Linked to Low \(\gamma\)-Linolenic Acid

The complexity of atopic dermatitis, an allergic skin disease, has made it especially difficult to find effective treatments and prevention strategies. Atopic dermatitis involves interactions among environmental, genetic, immunologic, biochemical and dietary factors. It has been known for many years that polyunsaturated fatty acid (PUFA) metabolism is perturbed in patients with atopic dermatitis, although findings are inconsistent and appear to be associated with immunoglobulin E (IgE) levels. A frequent observation is increased concentrations of linoleic acid and reduced levels of \(\gamma\)-linolenic acid, the first desaturation product of linoleic acid. Studies providing \(\gamma\)-linolenic acid to patients with the condition have reported improved outcomes. Reduction in long-chain omega-3 PUFAs (n-3 LC-PUFAs) has been reported in atopic dermatitis, but trials in which exposure to n-3 LC-PUFAs was increased have reported only modest results, if any.

Phospholipids of the epidermis are significantly increased in the condition, with a notable decrease in omega-6 (n-6) PUFAs, especially arachidonic acid. Free arachidonic acid concentrations in epidermis, however, are significantly elevated, suggesting an abnormality in transformation of phospholipids to other lipid classes. Arachidonic acid serves as a substrate for cyclooxygenase and lipoxygenase enzymes whose products, prostaglandin \(E_2\) and leukotriene \(B_4\), are elevated. In contrast to these inflammatory derivatives, lipoxins derived from
arachidonic acid and n-3 LC-PUFAs have potent anti-inflammatory and anti-proliferative effects.

Another consequence of abnormal n-6 PUFA metabolism is impaired water barrier function of the skin. This abnormality is also characteristic of essential fatty acid deficiency, as described in the 1950s by Hugh Sinclair. Defective skin permeability contributes to the pathogenesis of atopic dermatitis and correlates with disease severity and sensitization to aeroallergens. Arachidonic acid and its oxygenated derivatives are also needed for water barrier formation and healthy skin. The biosynthesis of free ceramides and the concentrations of fatty acids of more than 25 carbons are also significantly decreased in atopic dermatitis and these aberrations contribute to impaired epidermal barrier function. A report in elderly volunteers found that the consumption of borage oil providing 360 or 720 mg/day of γ-linolenic acid was associated with improved epidermal barrier function, reduced itch and an 11% decrease in transepidermal water loss.

In the observational studies described here, investigators examined the skin barrier function in children with atopic dermatitis and compared the findings with children having other atopic diseases and with nonatopic controls. Chiung-Hui Yen and colleagues at the National Taiwan University compared different groups of children and adolescents who had atopic diseases—dermatitis, asthma or rhinitis—with nonatopic controls for their serum fatty acids, severity of dermatitis and transdermal water loss. All patients had serum IgE levels greater than 150 U/mL. Recently published reference values (95th percentile) for non-smoking adults are 148 and 169 U/mL for women and men, respectively. Severity of dermatitis was scored by a single dermatologist, according to the Scoring Atopic Dermatitis (SCORAD) criteria developed in 1993 by the European Task Force on Atopic Dermatitis. Participants included 101 young people aged 2 to 17 years, 35 with atopic dermatitis, 35 with either atopic asthma or rhinitis, and 31 nonatopic controls. Fourteen dermatitis patients had SCORAD levels of at least 50, where the maximum score is 103. The SCORAD index is based on the extent, intensity and subjective symptoms of the patient’s lesions.

Serum fatty acid analyses documented no significant differences among the groups in linoleic or arachidonic acid concentrations. Both groups of atopic patients had significantly lower concentrations of γ-linolenic acid and dihomo-γ-linolenic acid compared with controls, but there was no significant difference in these fatty acids between atopic dermatitis patients and those with either asthma or rhinitis (Figure). Differences in these fatty acid levels between the asthma or rhinitis patients and controls, while lower, did not reach significance.

Transepidermal water loss was assessed on the right volar (palm side) forearm in patients with atopic dermatitis using a Tewameter™ 300 instrument and expressed as loss of water in g/m²/hr. Significant inverse associations were observed between transepidermal water loss and serum γ-linolenic acid and its derivative, dihomo-γ-linolenic acid and between SCORAD assessments and both fatty acids. Thus, water loss and clinical severity were lowest in dermatitis patients with the highest levels of these two n-6 PUFAs. Arachidonic acid concentration was unrelated to these parameters. Regrettably, the investigators did not report the serum concentrations of n-3 PUFAs.

Jayanta Gupta and colleagues at the University of Cincinnati College of Medicine, USA, investigated the disease severity and skin barrier function in African-American and Caucasian children with atopic dermatitis. They report that children with atopic dermatitis have inherently compromised skin barrier function as assessed by the Tewameter™ 300 device and that epidermal water loss was related to the severity of the disease assessed using SCORAD. Children with asthma or rhinitis did not have impaired skin barrier function.

Figure. Serum γ- (GLA) and dihomo-γ-linolenic acid (DGLA) concentrations (µmol/L) in patients with atopic dermatitis or asthma and controls.
These studies support the view that impaired skin permeability is a primary characteristic of atopic dermatitis. It is directly linked to studies more than 50 years ago on the importance of essential fatty acids in maintaining the epidermal permeability barrier. Reductions in skin barrier function exacerbate atopic dermatitis, undermine protection from ultraviolet light and interfere with the skin’s antimicrobial function. How to harness the importance of PUFAs in alleviating atopic dermatitis, however, remains elusive.


Rheumatoid Arthritis

Marine Omega-3 PUFAs Reduce NSAID Use in Patients with Rheumatoid Arthritis

Rheumatoid arthritis is a highly inflammatory, chronic autoimmune disease of the joints, characterized by painful swollen joints. It can progress to joint destruction, deformity and disability. The condition afflicts women 2 to 3 times more frequently than men, usually after age 55. There is no cure and treatment focuses on managing pain and retarding disease progression. Recent concern about the side effects associated with non-steroidal anti-inflammatory drugs (NSAIDs), widely used to ease pain, has shifted attention to less harmful agents, particularly long-chain omega-3 fatty acids (n-3 LC-PUFAs). Because of their anti-inflammatory effects, n-3 LC-PUFAs in gram quantities have been used successfully to treat patients with rheumatoid arthritis. Although some trials have observed no clinical benefits with n-3 LC-PUFAs given at <2 g/day, it is important to furnish a sufficient dose, usually 3 g/day or more. In addition to improving the patient’s clinical condition, consumption of fish oils may permit a reduction in the amount of NSAIDs needed to control pain or end their use. Additional benefits of adjunct therapy with n-3 LC-PUFAs or fish oil in rheumatoid arthritis patients should be a lower risk of cardiovascular disease and minimal, if any, gastrointestinal side effects.

At the end of 9 months, significantly more patients consuming the n-3 LC-PUFAs (19 of 49 or 39%) compared with those on the placebo (5 of 48 or 10%) reduced their daily NSAID requirement by more than 30% (Figure). On average, the reduction in NSAIDs was greater in the treated patients (26%) compared with the controls (9%). When results of only those patients who completed the study were analyzed, 19 of 32 (59%) treated patients reduced their need for NSAIDs by >30% compared with 5 of 26 control patients (19%). The difference between groups was

Patients were randomized to consume 10 capsules/day of a blend of cod liver and fish oil providing a total of 1.5 g eicosapentaenoic acid (EPA) and 700 mg docosahexaenoic acid (DHA) or air-filled placebo capsules for 9 months. Treatment supplements also contained vitamins A, D and E at levels equal to or below the US Dietary Reference Intakes. Patients were clinically assessed at baseline, 4, 12, 24 and 36 weeks. Patients recorded their daily doses of NSAIDs throughout the study and were encouraged to reduce their dose from the 12th week forward. The primary outcome measure was reduction of NSAID use by >30%. Fifty-eight participants (60%) completed the 9-month study.

Recent concern about the side effects associated with non-steroidal anti-inflammatory drugs, widely used to ease pain in rheumatoid arthritis, has shifted attention to less harmful agents, particularly long-chain omega-3 fatty acids.

Figure. Achievement of 30% or greater reduction in the average daily daily dose of NSAIDs in treated and control patients with rheumatoid arthritis. Image © B. Galarraga et al., from Rheumatology 2008;47:665-669, courtesy of Rheumatology.
statistically significant, P=0.002, in intention-to-treat analysis. Those consuming n-3 LC-PUFAs reduced their NSAID requirement by an average of 40%, while those taking the placebo reduced their NSAID use by 16%. Results were similar, but slightly strengthened, when the analysis was restricted to patients who did not increase their dose of other medications.

Clinical assessments revealed that the reduction in NSAID use was achieved without a worsening of disease activity or a significant increase in the use of other disease-modifying drugs. In fact, there was a small, but significant, improvement in the mean changes from baseline in the visual analog scores for pain at 9 months in patients taking the n-3 LC-PUFAs (-6.7 ± 3.1 SEM mm) compared with the placebo patients (1.9 ± 2.4 SEM mm). Other clinical assessments of both groups did not improve over the course of the study. Reported side effects were mild—nausea, vomiting, diarrhea, flatulence, inability to swallow the capsules—and did not differ between the groups. Reasons for patient withdrawal from the study did not differ between the groups and included adverse events related and unrelated to the study medication, voluntary withdrawal and lack of efficacy of the study medication.

These findings confirm the efficacy of n-3 LC-PUFAs at >2 g/day as an adjunct treatment for patients with rheumatoid arthritis. The study showed a significant decrease in the use of NSAIDs—39% of patients who started the study reduced their need for NSAIDs by more than a third and almost two-thirds of patients who completed the study achieved this reduction. With a substantial number of serious adverse effects associated with taking NSAIDs, these findings buttress previous reports that, for many patients, dependence on this class of drugs can be substantially reduced or avoided by taking n-3 LC-PUFAs or fish/cod liver oils. This study also confirms the need to allow sufficient time for improvements to accrue. Significant reduction in NSAID use was observed at 24 weeks, but not at 12 weeks. Others have reported that the maximum effect of fish oil on the reduction in NSAID medication was not observed until 12 months. Patients complained about the large number (10/day) and size of the capsules, but other investigators have circumvented this problem by using liquid fish oil or more concentrated supplements.

Use of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) in perinatal and postpartum depression is appealing because of their safety, beneficial effects on pregnancy outcomes and infant neurodevelopment, and usefulness in counteracting the depletion of maternal docosahexaenoic acid (DHA) stores. However, their effectiveness in treating postpartum depression remains uncertain and existing data are limited by small sample sizes, different treatments and doses, and confounding variables. Sufficient promising data have been published to warrant larger trials.

Two recent randomized, placebo-controlled studies examined the effectiveness of n-3 LC-PUFAs in women clinically diagnosed with major depressive disorder during pregnancy or postpartum. No participants in either

At the end of 9 months, significantly more patients consuming the n-3 LC-PUFAs (19 of 49 or 39%) compared with those on the placebo (5 of 48 or 10%) reduced their daily NSAID requirement by more than 30%.

It should be noted that the treatment also included fat-soluble vitamins that were not provided to the control group. Thus, these results may have been influenced by these nutrients as well. As the evidence accumulates, clinicians can consider fish oil as a front line treatment for patients with rheumatoid arthritis that improves their symptoms, reduces NSAID use and provides collateral health benefits.


MENTAL HEALTH

Depression

Omega-3 Supplementation in Pregnant or Perinatal Women: Two Studies, Two Results

Perinatal depression, the experience of major depressive disorder before or after pregnancy, jeopardizes the welfare of the mother and her infant. It is estimated that 10% to 15% of childbearing women giving birth experience postpartum depression, and there is a similar prevalence during pregnancy. While there are some treatment options for perinatal and postpartum depression, there have been heightened concerns recently about the use of antidepressants in pregnancy, which may limit their use.

There are some treatment options for perinatal and postpartum depression, but concerns about antidepressants in pregnancy limit their use. A safer alternative, n-3 LC-PUFAs, appear promising, but of uncertain effectiveness. Two new studies show why.

Use of long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) in perinatal and postpartum depression is appealing because of their safety, beneficial effects on pregnancy outcomes and infant neurodevelopment, and usefulness in counteracting the depletion of maternal docosahexaenoic acid (DHA) stores. However, their effectiveness in treating postpartum depression remains uncertain and existing data are limited by small sample sizes, different treatments and doses, and confounding variables. Sufficient promising data have been published to warrant larger trials.

Two recent randomized, placebo-controlled studies examined the effectiveness of n-3 LC-PUFAs in women clinically diagnosed with major depressive disorder during pregnancy or postpartum. No participants in either
study were taking antidepressant medications and none were diagnosed with bipolar disorder, psychotic disorder or substance abuse. All participants were free of current psychotropic medications. The study by Marlene Freeman and colleagues included women with perinatal depression, who experienced major depressive disorder during pregnancy and were enrolled by 32 weeks’ gestation, or who presented with postpartum depression within 4 weeks of delivery. Twenty-one pregnant and 30 postpartum participants completed at least 2 assessments. Due to ethical considerations of including a placebo-only group in a vulnerable population, all women received individual supportive psychotherapy during the study, provided as six 30-minute sessions.

In contrast, the study of Kuan-Pin Su and colleagues enrolled only pregnant women who were between their 16th and 32nd week of gestation. Thirty-six women participated, of whom 33 completed at least 2 evaluations. Similar depression assessment scales were used in this study, with the addition of the Beck Depression Inventory. All tests were administered every 2 weeks. Doses of n-3 LC-PUFAs differed between the 2 studies. Freeman used 1.9 g and Su used 3.4 g of n-3 LC-PUFAs/day, with both studies continuing for 8 weeks.

Women in the Freeman study were randomized to receive 1.9 g/day of n-3 LC-PUFAs (1.1 g eicosapentaenoic acid, EPA and 800 mg DHA) or corn oil placebo masked with 1% fish oil. Twenty-three women received placebo capsules and 28 were given the n-3 LC-PUFAs. Participants completed the Edinburgh Postnatal Depression Rating Scale at baseline and every 2 weeks thereafter. A clinician completed the Hamilton Rating Scale for Depression and the Clinical Global Impression Scale. The latter assesses global response to treatment. Participants in both groups did not differ in their depression scores at baseline and both groups had very low fish intake, <0.5 servings/mo. Pregnant participants were more likely than postpartum women to have previous antidepressant trials and a sibling with depression. Women in the n-3 LC-PUFA group were more likely to have a personal history of depression (1.5 prior medications for depression) compared with those in the placebo group (0.8 medications).

After 8 weeks, both groups experienced significant decreases in their Edinburgh and Hamilton scores compared with baseline assessments, but there were no significant differences between the groups (Table). Noting the change from baseline in both groups, the psychotherapy intervention appeared to have efficacy for perinatal depression. There were some differences in samples between the pregnant and postpartum patients, indicating that it may be difficult to study both groups in one study.

Small studies of standard antidepressant medications usually require large sample sizes to detect a difference between antidepressants and placebo. Therefore, the small sample size and the use of n-3 LC-PUFAs as an adjunct to a treatment that appeared efficacious in its own right limits the findings of this study. The investigators noted that the n-3 LC-PUFA capsules were well tolerated by both pregnant and postpartum women and strong interest in n-3 LC-PUFAs as a treatment for perinatal depression facilitated the initial recruitment for this pilot study. Although the majority of studies on perinatal depression suggest a benefit of n-3 LC-PUFAs, the dose, specificity of n-3 LC-PUFAs and prior n-3 LC-PUFA status may be important. In patients with low habitual fish consumption, it is possible that 8 weeks of n-3 LC-PUFA consumption was insufficient to meet maternal needs and address possible nervous system deficits that may have accumulated over a long time.

**Table. Depression scores (mean ± SD) in women with major depression consuming n-3 LC-PUFAs (1.9 g/day) or a placebo for 8 weeks during pregnancy or within 6 months of delivery**

<table>
<thead>
<tr>
<th>Assessment and participant</th>
<th>Placebo</th>
<th>Placebo</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Initial</td>
<td>Final</td>
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<tr>
<td><strong>Edinburgh Score</strong></td>
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<tr>
<td>Pregnant</td>
<td>9</td>
<td>15.8 (4.7)</td>
<td>7.8 (4.1)</td>
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<tr>
<td>Postpartum</td>
<td>14</td>
<td>15.9 (2.9)</td>
<td>8.3 (5.6)</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>15.3 (3.6)</td>
<td>8.1 (5.0)</td>
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<td><strong>Hamilton Score</strong></td>
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<td></td>
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<tr>
<td>Pregnant</td>
<td>9</td>
<td>16.2 (1.2)</td>
<td>10.2 (3.7)</td>
</tr>
<tr>
<td>Postpartum</td>
<td>14</td>
<td>18.2 (2.4)</td>
<td>9.7 (5.4)</td>
</tr>
<tr>
<td>Total</td>
<td>23</td>
<td>17.4 (2.2)</td>
<td>9.9 (4.7)</td>
</tr>
</tbody>
</table>
In the Su study, the primary outcome assessment was the change in the Hamilton Rating Scale score, with respondents defined as those with at least 50% improvement in score from baseline. Those with remission were defined as having a score of 7 or less. At the end of 8 weeks, women consuming the n-3 LC-PUFAs experienced a significant increase in their red blood cell DHA content from baseline (3.5% to 5.4%), but the increase in EPA (2.9% to 3.8%) did not reach statistical significance. After 8 weeks, the Hamilton Depression Rating scores decreased in both placebo and n-3 LC-PUFA groups, but the decrease was significant only in the n-3 LC-PUFA-treated women. The difference between the two groups was significant after 6 weeks. There were also significant decreases in the active treatment group in the Edinburgh and Beck scores at week 8. Interestingly, the rate of remissions was also higher in the n-3 LC-PUFA group, but the differences between the placebo and treatment groups were not statistically significant.

These two well designed clinical trials examined the effect of n-3 LC-PUFA supplementation in pregnant or postpartum women with major depression, only one reported a significant treatment benefit. A higher dose or the exclusion of postpartum depression may have contributed to the different outcomes.

So, readers are left with more questions. Are n-3 LC-PUFAs helpful to women in the perinatal period who are struggling with depression? These results provide some evidence that if consumed in sufficient amounts, n-3 LC-PUFAs may be beneficial. They also highlight the usefulness of psychotherapy. These fatty acids, which are usually under-consumed in western diets, are without serious adverse effects, and may benefit both mothers and the infants. These studies confirm that researchers continue to investigate the use of these nutrients in depressed women during the stressful perinatal period. Freeman's comments about the complexities of research in perinatal depression, the difficulties in recruiting and retaining participants, the interpretation of small trials with confounding factors and the larger picture of the psychosocial aspects of pregnancy are worth pondering.


EPA Plus Prozac Better than Either Treatment Alone for Major Depression

Long-chain omega-3 polyunsaturated fatty acids (n-3 LC-PUFAs) have been used as an adjunct therapy in treating patients with major depressive disorder with mixed, but often encouraging, results. A meta-analysis of placebo-controlled trials concluded that n-3 PUFAs have significant antidepressant effects, but there are insufficient data to distinguish whether combined treatment with the two major n-3 LC-PUFAs in fish oils, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), or each fatty acid given individually provides greater benefit. Studies have tended to find positive results with EPA rather than DHA and a rationale for this observation has been suggested. In most, if not all, trials to date, n-3 LC-PUFAs have been provided in conjunction with current antidepressant medications. Difficulties with patient compliance, unwanted or adverse side effects of medications and resistance to treatment make treating depression especially challenging.

Treatment of major depression with either EPA or fluoxetine (Prozac) improved responses in at least half the patients assessed, but treatment with both significantly improved the depression scores of 80% of patients by 4 weeks. Improvements continued through 8 weeks.
In this study, Shima Jazayeri and colleagues at the Tehran University of Medical Sciences in Iran sought to evaluate the effectiveness of fluoxetine (Prozac), EPA or a combination of them in patients with major depressive disorder as indicated by Hamilton Depression Rating Scale scores of 15 or greater. Patients did not have other psychiatric disorders or any other significant medical problems or substance abuse. They were not taking n-3 PUFA supplements nor eating more than one serving of fish/week. All participants were free of medication for at least 6 weeks prior to enrolment.

Sixty patients were recruited from referrals to the Roozbeh Psychiatric Hospital in Tehran and randomized to consume 20 mg of fluoxetine or 1 g EPA or a combination daily for 8 weeks. Each participant consumed either a fluoxetine placebo or a rapeseed oil placebo to mimic the type of capsules taken in each group. No placebo-only group was included for ethical reasons. Patients were assessed by the Hamilton Scales at baseline and every 2 weeks thereafter. Of the 60 patients enrolled, 48 completed at least 4 weeks of the study.

Over the course of the 8-week study, all patient groups exhibited significant reductions in their Hamilton depression scores as early as 2 weeks from baseline. Scores for patients treated with fluoxetine or EPA did not differ throughout the study. At 4 and 6 weeks, those consuming both EPA and fluoxetine showed a significantly greater improvement in their Hamilton ratings (as determined by analysis of covariance) compared with either treatment alone. Depression scores continued to improve from the 4th to the 8th week. Response rates for achieving at least a 50% reduction in depression score were 50% for fluoxetine, 56% for EPA and 81% for those taking both fluoxetine and EPA. More adverse events occurred in the fluoxetine and combination groups than in the EPA group and ranged from gastrointestinal effects, anxiety and decreased appetite to single reports of tremor, nightmare and constipation.

These results suggest a greater improvement in depression with the combination of EPA and fluoxetine, but the effects of either one alone may have been no different from a placebo, had there been one. Other studies have reported a placebo effect of trial participation. This study supports those that have reported significant improvement in depression using a modest dose (1 g/day) of EPA as an adjunct treatment to current medication.

The primary outcome was time to reverse cholestasis, defined as the first of 3 consecutive bilirubin measurements ≤2 mg/dL, while still receiving TPN. Efficacy of treatment was assessed only in infants who survived and did not undergo liver transplantation. Patients in both groups who did not reverse cholestasis were censored and bilirubin levels imputed if 2 or more consecutive bilirubin measurements were missing. At enrollment 8 weeks prior to treatment, infants in the fish oil group had shorter gestation, fewer enteral calories and higher direct bilirubin levels, although only gestation time was significantly different from the historical group. These observations suggest that treated infants were more severely ill than those in the historical group. Both groups had similar rates of bilirubin increase prior to treatment and for up to 4 weeks after treatment. Patients were monitored from baseline for up to 36 weeks, with the median time being 18.4 weeks.

Of the 39 infants in the study, 9 died, 2 in the fish oil group and 7 in the historical group. None of the deaths in the fish oil group and 6 in the comparison group were from liver-related causes. Risk of death in the fish oil and historical groups was 11% and 33%, respectively, but this difference was not statistically significant.

In the whole patient group, 21 never reversed cholestasis, including those who died. Among the survivors, the median time to ending TPN was 14 weeks in the fish oil group and 23 weeks in the soybean oil group. Perhaps more important, the median time to reverse cholestasis was 9 weeks in the fish oil group and 44 weeks in the soybean oil historical group ($P=0.002$). Survivors who were treated with fish oil were nearly 5 times as likely to reverse cholestasis as those in the historical group (Table). When the data were adjusted for gestational age, baseline bilirubin level and necrotizing enterocolitis, the likelihood of reversing cholestasis was nearly 7 times higher with fish oil treatment. The odds of reversing cholestasis were 16 times more likely when the analysis included all those who enrolled and adjustment for confounding variables. Interestingly, additional reversals of cholestasis after TPN was discontinued occurred within 8 weeks (median 3 wk) in 5 patients treated with fish oil, but no reversals occurred in the soybean oil patients.

The authors noted that preterm infants may survive without lifelong dependence on TPN with as little as 11 cm of initial bowel length, but survival is a race between bowel growth and the development of TPN-associated liver disease. If liver disease develops, the mortality rate can be 100% if the child remains on TPN for a year. Thus, the significantly improved chance of reversing cholestasis with fish oil TPN in these infants greatly increases their chance of survival. Reversal of the liver disease occurred more frequently and more quickly with fish oil than with soybean oil TPN, with median times of 9 and 44 weeks, respectively. Based on previous experience, the investigators observed that reversal of liver disease usually occurs once enteral feeding becomes established after TPN ends. In the fish oil infants, reversal occurred during TPN and in some cases, after. There were fewer deaths and transplantations in the fish oil group, as well.

This study provides clear evidence that a fish oil emulsion is significantly superior to one based on soybean oil in reversing parenteral nutrition-associated liver disease in infants with cholestasis. The fish oil emulsion achieved positive outcomes more quickly and more often and was without deleterious effects. Some infants receiving the soybean oil emulsion did reverse

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**Table. Increased likelihood of reversing cholestasis with TPN containing fish oil vs soybean oil**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Survivors, n=30</th>
<th>All patients, n=39</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard ratio (95% CI)</td>
<td>Hazard ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Crude estimate</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish vs soybean oil</td>
<td>4.8 (1.6 - 14.1)</td>
<td>7.9 (2.6 – 24.0)</td>
</tr>
<tr>
<td><strong>Adjusted estimates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish vs soybean oil</td>
<td>6.8 (1.7 - 27.8)</td>
<td>15.9 (3.7 – 68.4)</td>
</tr>
<tr>
<td>Gestational age</td>
<td>0.82 (0.63 – 1.07)</td>
<td>0.92 (0.74 – 1.14)</td>
</tr>
<tr>
<td>Bilirubin at baseline</td>
<td>0.78 (0.58 – 1.06)</td>
<td>0.85 (0.65 – 1.12)</td>
</tr>
<tr>
<td>NEC*</td>
<td>0.06 (0.004 – 0.770)</td>
<td>0.15 (0.02 – 1.29)</td>
</tr>
</tbody>
</table>

*NEC, necrotizing enterocolitis*
their cholestasis, but more died than among those receiving fish oil. In their discussion, the authors suggested that phytosterols in the soybean oil emulsions might have toxic effects on the liver and their high content of n-6 PUFAs likely contribute to impaired immune function and enhanced inflammation. With these findings, it appears unjustifiable to provide TPN patients with emulsions lacking LC-PUFAs, especially those of the n-3 family.


TPN with Fish Oil Hastens Reduction in C-Reactive Protein in Acute Pancreatitis

Critically ill patients, such as those recovering from gastrointestinal surgery, trauma, sepsis or other major illnesses, usually receive nutritional support from total parenteral nutrition (TPN). Solutions used must furnish all essential nutrients and sufficient energy to prevent excessive weight loss and meet the increased metabolic demands of illness.

The need to meet essential fatty acid requirements was recognized in 1981, when symptoms of deficiency were reported. The following year, alpha-linolenic acid (ALA) deficiency was reported in a patient maintained on a gastric tube feeding that provided 76% linoleic acid and 0.7% ALA. By 1986 it was recognized that parenteral solutions providing high levels of linoleic acid with little ALA were associated with reduced levels of long-chain polyunsaturated fatty acids (LC-PUFAs). Early lipid emulsions for parenteral feeding were based on soybean oil containing both linoleic acid and ALA, usually in a ratio of about 7:1. In the U.S., only soybean oil parenteral feedings are approved for medical use, although one with fish oil may be used with special approval. In several European countries, at least one lipid emulsion containing fish oil may be used and another has been developed. The composition and immunological effects of these products have been reviewed.

In addition to concerns about LC-PUFAs and the lack of omega-3 (n-3) LC-PUFAs, the fatty acid composition of TPN emulsions affects immune function by influencing membrane structure and function, the production of eicosanoids and lipoxins that have potent effects on inflammation, and the regulation of gene expression and cell survival. Many of the effects of n-3 and n-6 LC-PUFAs counteract each other, while others are complementary. Because patients on TPN are highly vulnerable to infection, LC-PUFAs may enhance or reduce this susceptibility and directly affect patient recovery and survival. Dramatic improvements in the recovery of 2 infants with intestinal failure and liver disease were reported following the replacement of their soybean oil-based TPN preparation with a fish oil-based one.

Increased interest in n-3 LC-PUFAs in TPN has prompted investigation of their use in diverse clinical conditions. Dr. Xinying Wang and colleagues at the Jinling Hospital, Nanjing, China, reported observations in 40 TPN-treated patients with severe acute pancreatitis. Patients were enrolled within 72 hours of the onset of pancreatitis and were randomized in double-blind fashion to receive TPN emulsions containing soybean oil or soybean oil plus fish oil (Table). Blood samples were taken at day 1 (baseline) before TPN was initiated and on day 6 after completion of TPN.

<table>
<thead>
<tr>
<th>Day</th>
<th>Both groups</th>
<th>Control</th>
<th>n-3 LC-PUFA Soybean+Fish oil*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.0</td>
<td>0.8</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>2-5</td>
<td>3.0</td>
<td>1.25</td>
<td>0.8 ± 0.2</td>
</tr>
</tbody>
</table>

*n-3 PUFAs replaced n-6 PUFAs up to 10 g/day

Primary outcome measures were infection morbidity, mortality, time in intensive care and days in the hospital. There were 28 men and 12 women in the groups, with an average age of about 40. TPN was well tolerated in both groups. At baseline and day 6, concentrations of IL-6, an inflammatory marker, were not statistically different between the groups. C-reactive protein concentrations were elevated above normal values at baseline in all patients, but on day 6, had decreased significantly in both groups, with the reduction significantly greater in the fish oil group.
For the primary outcomes, 5 patients had infectious complications in the control group and 3 in the fish oil group. Two deaths occurred among the controls, but none occurred in the fish oil group. The number of days in intensive care and the hospital were lower in the fish oil group, but the differences did not reach statistical significance. Both groups improved their respiratory function significantly with TPN, but the improvement was significantly greater in the fish oil group, as assessed by the oxygenation index, 35% vs 48% improvement in the control and fish oil groups, respectively. The number of days of continuous renal replacement therapy was significantly lower in the fish oil group compared with the control group, 18 vs 26 days.

In summary, patients with severe acute pancreatitis given soybean and fish oil emulsions exhibited some significantly better indices of recovery, such as greater reduction in C-reactive protein, better respiratory function and fewer days of renal replacement therapy, compared with patients given only soybean oil TPN.

Patients with severe acute pancreatitis given soybean with fish oil TPN emulsions exhibited significantly better indices of recovery, such as greater reduction in C-reactive protein, better respiratory function and fewer days of renal replacement therapy, compared with patients given only soybean oil TPN.

better indices of recovery compared with patients given only soybean oil emulsion—greater reduction in C-reactive protein, better respiratory function and fewer days of renal replacement therapy—but infectious complications, length of hospital stay, time in intensive care and other parameters showed only a trend to better outcomes. Thus, this study provides some evidence that the addition of n-3 LC-PUFAs to TPN emulsions has a moderating effect on the hyperinflammatory responses characteristic of severely ill patients.


Fish Oil TPN Reduces Interleukin-6 and Shortens Hospital Stay After Colorectal Surgery

Total parenteral nutrition (TPN) is commonly used in post-surgical patients to provide adequate nutrition and energy for recovery. A growing body of evidence suggests that the addition of long-chain omega-3 polysaturated fatty acids (n-3 LC-PUFAs) improves patient outcomes, although effects may be modest. In some instances of critically ill patients, provision of these fatty acids has been life-saving. Generally speaking, the addition of n-3 LC-PUFAs to parenteral and enteral nutrition benefits the patient by improving respiratory function and immune responses, reducing cardiovascular risks, and possibly reducing infections. However, a systematic review of fish oils in kidney transplant recipients concluded that there was too little evidence to recommend fish oil therapy to improve renal function or surgical outcomes. A clinical evaluation of a lipid emulsion enriched with n-3 LC-PUFAs from fish oil reported that the length of hospital stay was significantly reduced for patients recovering from major abdominal surgery. A reduction in infectious complications has been frequently reported with immunonutrition in surgery, but it is unclear whether specific agents or the combination of them contribute to patient improvement. The most common rationale for including n-3 LC-PUFAs in enteral and parenteral emulsions is to combat the inflammatory effects of the n-6 PUFAs that predominate in soybean oil preparations. Details of the immunomodulatory effects of parenteral lipids have been described recently.

With the advent of parenteral emulsions containing fish oils, it has become possible to compare patient outcomes in those given standard soybean oil TPN with those receiving soybean oil plus fish oil. In this report, Bin Liang and colleagues at the Peking University People’s Hospital, Beijing, China, compared a battery of immune responses, mortality, hospital stay and infectious complications in colorectal cancer patients receiving TPN with and without fish oil for 7 days following radical resection. The fish oil emulsion contained n-3 LC-PUFAs up to 0.2 g/kg body weight/day, substituted for n-6 PUFAs in the soybean oil emulsion. Both TPN preparations were equivalent in calories and nitrogen according to the patient’s body mass. Blood samples were obtained on the day before surgery and 1 and 8 days post-operatively.

The investigators measured the inflammatory cytokines IL-6 and TNF-α; T-cell surface proteins CD3+, CD4+ and CD8+; length of hospital stay and infectious complications. One patient withdrew from the study because of unresectable disease. There were no statistically significant differences in patient clinical characteristics or demographics at baseline. Of the 42 patients, 3 had stage 1 colorectal cancer, 20 stage 2 and 18 stage 3 disease.
Patient evaluations 7 days after surgery revealed no deaths in either group and one incision infection in each group. Fish oil-treated patients stayed in the hospital fewer days than soybean oil patients (17.4 vs 19.6 days), but these differences were not statistically significant. Patients receiving fish oil TPN had significantly lower concentrations of the inflammatory cytokine IL-6 compared with soybean oil patients, but changes in TNF-α did not reach statistical significance. There were no statistically significant changes in any T-cell surface receptor proteins, but the increase in the ratio of CD4+ to CD8+ with the fish oil TPN was significant.

This report is consistent with the preceding report in patients with acute pancreatitis in observing significant reductions in IL-6 with fish oil TPN. Both studies reported results suggestive of reduced inflammation and shorter hospital stays. Treatment with TPN was short in both studies, so that differences in patient outcomes would be limited to immediate post-surgical effects. One might speculate that continued provision of n-3 LC-PUFAs during recovery might hasten recuperation and further reduce the consequences of inflammation, in part owing to the production of resolvins derived from n-3 LC-PUFAs.