SeaHealthUCD

Issue 27A: April, 2018: This is a supplement to SeaHealth-ucd Issue 27

Update on omega-3s and health

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Consumers are increasingly aware of the health benefits of oily fish via social and other media and through promotions by health professionals and supermarkets (Slattery & Gormley, 2013). Farmed salmon is often the oily fish of choice for consumers due to its ready availability and the dwindling supplies of wild oily fish. Hence the importance of the current study, which was a snapshot in time of the polyunsaturated fatty acid (PUFA) status of raw farmed salmon on sale in retail outlets in Dublin and vicinity and is reported in a sister publication *SeaHealth-ucd Issue 27B April 2018*. The study commenced with a survey of the health benefits of omega-3 PUFAs with emphasis on recent developments and these are outlined here. The health benefits of PUFAs were first detected in the Eskimo population. It was observed that the Inuit had a very low incidence of arterial disease despite having a high fat diet comprised mainly of seafood and seal meat. Studies linked the high intake of EPA and DHA to beneficial effects on plasma lipid levels and a lower incidence of coronary artery atherosclerosis (Dyerberg *et al.,* 1975; McLaughlin *et al.,* 2005). Since then scientists and health professionals have published a plethora of scientific papers on the topic. These and popular articles derived from them have dramatically increased public awareness of the health benefits of PUFAs, especially eicosaptenaenoic (EPA) and docosahexaenoic (DHA) acids. PUFAs play a key role in regulating a wide range of functions in the body, such as blood pressure, blood clotting, brain development and function (Siriwardhana *et al.,* 2012; Wall *et al.,* 2010); they also have anti-inflammatory properties.

1. Essential fatty acids

Essential fatty acids cannot be synthesized by humans and thus must be supplied in the diet (Simopoulos, 2002). There are two main types i.e. the omega-6 and omega-3 series. The omega-6 series are derived from linoleic acid (LA; 18:2ω-6). Both LA and alpha linolenic acid (ALA; 18:3ω-3) are of plant origin and the latter is the precursor of omega-3 fatty acids EPA (20:5ω-3) and DHA (22:6ω-3). However, only very small quantities of ALA are converted *in-vivo* to EPA, and even less to DHA (Harris *et al.,* 2008). Oily fish has long been recognized as a major source of EPA and DHA (Siriwardhana *et al.,* 2012).

2. Anti-inflammatory properties of EPA & DHA

Inflammation is part of the normal host response to infection and injury. However, excessive inflammation contributes to a range of acute and chronic human diseases via the production of inflammatory cytokines and eicosanoids (prostaglandins, thromboxanes, leukotrienes). However, at sufficiently high intakes, omega-3 PUFAs, as found in oily fish and fish oils, decrease the production of these inflammatory compounds (Calder, 2006; Steffens, 1997; Wall *et al.,* 2010). Omega-3 PUFAs also give rise to a family of anti-inflammatory mediators termed resolvins. Thus, omega-3 PUFAs are potentially potent anti-inflammatory agents. The anti-inflammatory properties of EPA and DHA may beneficially alter the course of immune-mediated inflammatory conditions (Wanten and Calder, 2007). For example, sepsis is a common systematic inflammatory response syndrome that is induced by infection (Bone *et al.,* 1997). The mortality rate from sepsis is rising and currently 5.3 million deaths from sepsis occur each year (Fleischmann *et al.,* 2016). A recent study in China involving 112 patients with sepsis who received parenteral nutrition containing fish oil along with standard sepsis treatment resulted in a 20% reduction in all-cause mortality compared to a 10% reduction in the control group. Furthermore, the study group stay in the intensive care unit was shorter than the stay of the control group (Li *et al.,* 2018). This reduction in mortality with the incorporation of fish oils into parenteral nutrition may be a result of a reduced infiltration of inflammatory leukocytes and modulation of the cytokines released (Calder, 2004; Wanten and Calder, 2007; Mayer and Seeger, 2008). Furthermore, it is believed that the addition of fish oil to the parenteral nutrition will balance the negative effect of pro-inflammatory omega-6 PUFAs through endotoxin-induced stress response (Mayer and Seeger, 2008). Although there are some consistent data on clinical benefits of omega-3 PUFAs in chronic inflammatory conditions in clinically ill patients, the majority of trials have been conducted with small numbers of subjects and have not been randomized which may result in bias.

Parenteral nutrition bypasses the normal digestion in the stomach and bowel. It is a special liquid food mixture given into the blood through an intravenous catheter (needle in the vein). The mixture contains proteins, carbohydrates (sugars), fats, vitamins and minerals (such as calcium).

3. Omega 3/6 ratios & omega-3 and -6 intakes

Simopoulos (1991) suggested that the Western diet was deficient in omega-3 fatty acids with the omega-3/6 fatty acid ratio ranging from 1:10 to 1:25. The importance of the omega-3/6 ratio in the diet has been repeatedly demonstrated, and is frequently observed at 1/15-17 because of mass consumption of omega-6 rich vegetable oils (Simopoulos, 2016). In a secondary prevention trial of cardiovascular disease, a ratio of omega-3/6 fatty acids of 1:4 resulted in a 70% decrease in total mortality and on this basis was recommended as a desirable dietary target ratio (Simopoulos, 2002). Recommended intakes of EPA and DHA range widely as evidenced in *Global Recommendations for EPA and DHA Intake* (Revised 16 April 2014). The European Food Safety Authority (EFSA) recommends 250mg of EPA+DHA per day plus an additional 100–200mg DHA for pregnant women. The American Heart Association recommends eating a minimum of two servings of fish, preferably oily, per week for healthy adults to maintain cardiovascular function (Kris-Etherton *et al.,* 2003). An intake of 900mg/day of EPA+DHA reduced mortality in patients with coronary heart disease (CHD) (Krauss *et al.,* 2000). The International Society for the Study of Fatty Acids and Lipids (ISSFAL) recommend that adults have a minimum of 500mg of EPA+DHA per day to maintain cardiovascular functioning. Therefore, an EPA+DHA intake of circa 0.5g per day for an adult is a reasonable target based on current information. Eating oily fish is a preferred source to fish oil supplements and an average serving (~150g) of most oily fish will supply this amount. Inclusion of fish in the diet will help increase the omega-3/6 fatty acid ratio in the body without the need for supplementation thereby decreasing the incidence of chronic diseases involving the inflammatory process (Wall *et al.,* 2010; Simopoulos, 2002).

4. Omega-3s and cardiovascular disease (CVD)

CVD accounts for 17.3 million deaths per year, making it the leading global cause of death (Sacks *et al.,* 2017). There is huge global interest in preventative treatment of CVD in relation to improved human health and also to reducing the economic cost burden of treatment both in the short and long term. Current scientific information strongly associates oily fish in the diet with positive effects on cardiovascular health, via omega-3 PUFAs (Sacks *et al.,* 2017; Harris *et al.,* 2017). Hidayat *et al.* (2017) conducted a meta-analysis of 51 randomized control trials with approximately 3,000 participants. This provided strong clinical evidence on marine-derived omega-3 long chain PUFA supplements and their cardio-protective effect by reducing heart rate. Lentjes *et al.* (2017) studied the association between marine omega-3 supplement users and CHD. Seafood and supplement intake resulted in a 26% lower risk of CHD mortality after adjustment of supplementation for fish consumption compared with non-supplement users. Protective association was observed between omega-3 PUFA supplement use and CHD mortality when fish consumption was low.

4.1 Omega-3 Index (O3I): Most studies on CHD and the potential benefits of omega-3 PUFAs look at self-reported consumption of fish rather than at specific biomarkers. Red blood cell membranes may be used as a biomarker for assessing long chain omega-3 fatty acid status in humans (Harris, 2008). Red blood cell membranes carry EPA and DHA around the body and the omega-3 Index (O3I) is defined as the ratio of EPA plus DHA divided by total fatty acid content in red blood cell membranes multiplied by 100. O3I has emerged in recent years to act as a risk factor for CHD mortality and Harris *et al.* (2017) undertook a secondary analysis of 10 cohort studies to look at individual omega-3 PUFA levels and separate them into O3I quintiles and the relative risk for CHD. Highest risk prevailed at O3I <4%, an intermediate risk between 4 to 8% and lowest risk at >8%. These findings support the use of <4% and >8% as therapeutic targets for O31 (Harris *et al.,* 2017). These cut off points agreed with a previous study based on information available at the time (Harris and von Schacky, 2004). They concluded that having an O3I <4% was associated with a 15% increase in risk of CHD mortality, whereas, having an O3I >8% reduced the relative risk for fatal CHD by approximately 30%. Furthermore, a study among 2,500 participants from the long-running Framingham Heart Study showed that O3I was inversely associated with mortality and incident CVD (Harris *et al.,* 2018). Similarly, like the previous study, those who were in the highest O3I quintiles (>6.8%) compared to O31 of <4.2% had a 34% lower risk of fatal CVD and a 39% lower risk for a CVD incident.

Omega-3 PUFAs are not uniform in their cardio-protective effects: for example, DHA has a greater effect than EPA on reducing heart rate (Hidayat *et al.,* 2017). Similarly, Del Gobbo *et al.* (2016) also observed this when evaluating omega-3 PUFA biomarkers for the primary prevention of CHD in 19 cohort studies. DHA was associated with the lowest risk of CHD compared to EPA, ALA and docosapentaenoic acid (DPA; 22:5ω-3) respectively. In omega-3 index quintile analysis, ALA or DPA were not significantly related to any measured outcome of CVD (Harris *et al.,* 2017). Although in recent studies there is a positive trend in DPA's potential as an important bioactive fatty acid (Kaur *et al.,* 2016; Del Gobbo *et al.,* 2016). The mechanisms responsible for the observed effects of omega-3 fatty acids on cardiovascular health lack strong scientific evidence. Hypertriglyceridemia is a condition where elevated levels of triglycerides in the blood are associated with atherosclerosis. The hypotriglyceridemic effects of omega-3 fatty acids from fish oils is well established and 2-4g of EPA+DHA per day can lower triglycerides by 20 to 40% (Kris-Etherton *et al.,* 2003). Significant reductions in triglycerides were also found in patients with type 2 diabetes (Montori *et al.,* 2000). However, as the effective dose of omega-3 fatty acids is quite high, this amount can only be obtained consistently by supplementation. On a cautionary note excessive consumption of omega-3 supplements could result in excessive bleeding in some individuals and it may be a case that too much is as bad as too little (Kris-Etherton *et al.,* 2002).

5. Omega-3s and blood pressure

EPA inhibits the conversion of angiotensin I to angiotensin II (ACE inhibition) by disturbing the generation of the highly pro-inflammatory prostaglandin E_2 and increases E_3 instead (Calder, 2004; Siriwardhana *et al.,* 2012). This results in a reduction in blood pressure and can help maintain blood vessel dilation. Furthermore, EPA/DHA reduce the level of platelet aggregation in the blood thus acting as a blood thinner which reduces the likelihood of clot formation (Harris *et al.,* 2008). Therefore, consumption of fish to obtain omega-3 PUFAs should be encouraged for the multiple health benefits arising from their anti-inflammatory actions.

6. Omega-3s and brain development/health

There is extensive ongoing research on the effect of omega-3 PUFAs on brain health and neurodevelopment and the topic has been reviewed recently by Dyall (2015). Neurodevelopment refers to the brain and central nervous system which influences function, emotion, learning ability, memory and long-term cognitive health (Gormley, 2012a). DHA supplementation during pregnancy, lactation or childhood may play an important role in enhancing neuronal development (Makrides *et al.,* 2010; Ryan *et al.,* 2010). For pre-term infants, DHA supplementation has a beneficial effect on cognitive development at 12 months of age but the benefits of supplementation of children older than 2 years showed inconclusive evidence of increased cognitive performance (Eilander *et al.,* 2007). In underperforming school children aged 7 to 9 years old, no beneficial effect from supplementation was observed on reading, memory or behavior which contradicts previous trials (Montgomery *et al.,* 2018). In young adults (18-29 years old), supplementation with DHA increased blood flow to the brain but did not improve performance in solving computerized cognitive tasks (Jackson *et al.,* 2012). In the elderly, an increase in the intake of DHA decreased the progression of neurodegenerative disorders. An improved performance on neuropsychological tests of the frontal lobe functioning was observed in older men and women with higher serum omega-3 PUFAs (D'Ascoli *et al.,* 2016). Although considerable research has been done on the positive effects of fish oil supplementation on cognitive functioning, further studies are needed before a definitive statement can be made.

7. Omega-3s in eye development & health

DHA is found in high concentration in the retina, where it acts as a structural lipid (McCusker *et al.,* 2016). In the last trimester of pregnancy and up to 2 years of age, DHA is rapidly incorporated in the nervous tissue of the retina and the brain. Supplementation of pre-term infants and the effect on visual development was inconclusive, whereas high dose supplementation of long chain PUFAs in full term infants, showed consistent evidence of a beneficial effect on visual development during the first year of life (Eilander *et al.,* 2007). In older people, age-related macular degeneration (AMD) occurs when a small central part of the retina deteriorates with age. Some studies suggest people who consume higher amounts of EPA and DHA (at least 1 portion of fish per week) have a lower risk of developing early AMD (Tan *et al.,* 2009; Augood *et al.,* 2008).

8. Availability & sustainability of fish oils

Fish lipids are an invaluable source of EPA and DHA (Merdzhanova *et al.,* 2017). Quantities vary among and within species and are subject to environmental variables such as maturity, time of season, diet and whether fish are wild or farmed. It takes circa 3-5kg of small oily fish (e.g. sprat, anchovies) to produce 1kg of farmed salmon (Gormley, 2012b); obviously this is not sustainable in the medium or long term. As the demand for carnivorous fish species continues there is an increased demand for fish meal and, therefore, fish oil. About 6.2 to 7.4 million tonnes of fish meal and 1.0 to 1.7 million tonnes of fish oil are produced each year (Pickova and Morkore, 2007). Plant derived oils in addition to marine oils are being used in fish feed for economic and environmental sustainability reasons. Fish diet strategies have been developed where a plant oil-based diet is fed during the growing phase and subsequently replaced by a fish oil-based diet prior to harvesting thus boosting EPA and DHA content. In 2008 it was estimated that salmon feeds contained around 230g/kg of fish oil, but by 2020 salmon grower feeds are projected to contain only 80g/kg fish oil of the total diet formula (Tacon and Metian, 2008).

Farmed freshwater fish species can also serve as a valuable source of EPA and DHA provided their feed contains an adequate amount of marine fish oil. However, they also contain a substantially higher level of LA due to the use of a vegetable oil component in their feed in addition to marine fish oil (Steffens, 1997; Steffens and Wirth, 2005). As a result the omega-3/6 ratio is lower for farmed freshwater fish compared to wild marine fish and this may have a negative effect (lowering) on the O3I in some individuals.

The growing demand for oils rich in EPA & DHA both for fish feeds and supplements for humans will continue. Both salmon farming and nutraceutical markets are expected to grow strongly over the next few years while fish oil production is expected to remain largely static. Krill is a major source of EPA and DHA and the Antarctic krill biomass was estimated at 200-400 million tonnes in 2013 with annual catches at that time of about 200k tonnes (Gormley, 2013). However, there has been heavy exploitation of krill stocks since then and the large biomass is being seriously depleted. Novel sources of EPA and DHA are expected to yield <50k tonnes of extra oil by 2017 – most of this coming from algae. Integrated production systems may be one of the ways forward i.e. farming of fish, molluscs and macro-algae side-by-side where the molluscs use waste from the cages, and macro-algae use some of the other by-products. Vegetable oil seeds which have been genetically modified to produce EPA and DHA in quantity also have potential. Currently there is no commercial production of plant based EPA and DHA but the two species closest to market are soy and rapeseed (canola). Therefore, new and modified fermentation technologies which will reduce the cost of producing EPA and DHA from micro-algae are required and are being extensively researched worldwide (Gormley, 2013).

9. Acknowledgements

Sincere thanks to The Food Safety Authority of Ireland for part-funding this project.

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