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The role of Long Chain Fatty acid (n-3 PUFA) supplementation in Rheumatoid arthritis

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Introduction
There is an established link between fish oils and the treatment/ prevention of inflammatory, autoimmune diseases such as Rheumatoid Arthritis (RA), however there are currently no UK guidelines which promote their use in its treatment. I chose RA as a topic for this essay because I have given presentations on the matter during my B placement, and have discovered that a large proportion of the group were taking fish oil supplements. The aim of this essay is to gain a better understanding of the current evidence to support the use of fish oil supplements in RA.

RA is a chronic inflammatory, autoimmune disease that may be characterised by invasion of macrophages and T lymphocytes into synovial tissues, causing inflammation, damage to cartilage tissues, and the bones of hands and feet, muscle wasting, reduction in movement, strength and ability to perform daily tasks (Moghaddami *et al.,* 2007; Calder and Zurier, 2001). Individuals who have RA may also be more likely to develop cardio vascular disease, and osteoporosis (Rennie *et al.*, 2003). The primary treatment of RA is pharmacological, which often causes side effects such as gastro- intestinal bleeding, increased vascular risks and increased nutrient requirements or reduced absorption (NHS Institute for Innovation and Improvement, 2009; Rennie *et al*., 2003). It would be useful to know if fish oil supplementation could reduce polypharmacy in RA.

The role of n-3 PUFA's in the treatment of RA
A review by Rennie *et al*. (2003) discusses the role of polyunsaturated fatty acids (PUFA) in inflammation. n-3 and n-6 PUFA's, most predominately arachidonic acid (AA, n-6) are incorporated into phospho-lipid membranes. AA is thought to be a principle precursor for eicosanoid synthesis from inflammatory cells. These eicosanoids produce 2 series prostoglandins and 4 series leukotrienes, and are more pro inflammatory than Eicosapentaenoic Acid (EPA, n-3) derived eicosanoids of the 3 and 5 series (Calder and Zurier, 2001). EPA and Docosahexaenoic Acid (DHA) compete with AA for incorporation into phospho-lipid membranes, and conversion to pro-inflammatory eicosanoids. A higher level of PUFA n-3 in cell membranes can reduce the release of pro-inflammatory cytokines TNFα, interleukin 1β, and 6, proliferation of T lymphocytes and reactive oxygen species (ROS). It is therefore believed that a diet high in PUFA n-3 (EPA,

DHA) from fish oils has the potential to reduce symptoms of RA (Calder and Zurier, 2001; Pattison *et al*., 2004; Rennie *et al*., 2003).

Review of the evidence

According to Simpoulos and Cleland (2003) research into the benefits of oily fish stemmed from epidemiological studies which showed a lower incidence of RA and inflammatory diseases in populations that ate more than two portions of fish a week, such as Greenland Eskimo community (Harvald, 1989) . Further research has been carried out since. For instance Tempel et al. (1990) conducted a randomised double blind, placebo controlled, cross over trial whereby participants took 12 capsules daily of either fish oil (2.04g EPA, 1.32g DHA) or coconut oil with a fishy flavour as a placebo (capric acid 36mol%, caprylic acid 63mol%), for 12 weeks, and then crossed over. The results suggested an improvement in joint swelling, duration of early morning stiffness(EMS), and an improvement of the joint pain index score, however no improvement for the visual analogue pain scale score (VAS for pain) or grip strength was found. They also reported that incorporation of n-3 PUFA into the plasma cholesterol ester fraction increased, and reached a maximum after 1 month, the number of neutrophils decreased after 12 weeks, leucotriene β_5 production increased and the difference between placebo and fish oil treatment in joint pain index correlated with this increase.

Although they concluded that fish oils provided benefit to the symptoms and inflammatory components of RA there were some limitations which could have influenced the results. Firstly the placebo consisted of saturated fatty acids (SFA) which are known to have pro-inflammatory effects (Thomas and Bishop, 2007). The results would have been more valid if the placebo was neutral. Secondly there was no wash out period between the fish oil treatment and placebo. It was reported that there was some ‘hangover’ effect in treatment variables 4 weeks after the fish oil supplementation had stopped, therefore participants who started with the placebo could have experienced a hangover effect from the SFA, thus reducing the efficacy of the fish oil supplements, and the reliability of the results.

A later study by Volker et al. (2000) also investigated the effectiveness of fish oil supplementation (n=50) during a 15 week, randomized, placebo controlled, double blind trial, however this study chose a mixture of corn oil and olive oil as a placebo. Participants who had a background diet of <10g PUFA n-6, were randomised into groups that received either fish oil capsules (60% n-3) amounting to 40mg/kg body weight/day or the placebo. They found that 5 participants taking fish oils and 3 taking the placebo had improved by 20% according to American College of Rheumatology criteria, and clinical variables such as swollen joint count (SJC), duration of EMS, VAS of pain, patient and physician assessment of arthritis, and health assessment questionnaire (HAQ), had improved at 15 weeks for the fish oil group (there were no improvements at 4 or 8 weeks). Like Tempel (1990) there was also increased incorporation of EPA and DHA in phospho- lipid membranes. A key limitation of this study is that not all

results were presented and strengths and weaknesses of the study were not disclosed, so it is not known how significant or reliable these results were. It has been suggested that MUFA derived eicosatrienoic acid (ETA), competes in a similar way to n-3 PUFA by competing with n-6 PUFA for cell membrane incorporation (Rennie *et al*., 2003). It is therefore difficult to assess the full impact of fish oils when a potentially beneficial placebo is used. This study's results suggest a greater number of improvements in clinical characteristics compared to those of Tempel (1990); perhaps this is because the SFA placebo used in Tempel (1990) may have reduced the effectiveness of the fish oil supplements when taken after the placebo. Volker *et al*. (2000) also only included participants with <10g/day intake of n-6 PUFA, which may have reduced the baseline pro-inflammatory effects on the clinical characteristics, compared to Tempel (1990).

A study by Berbert *et al.* (2005) investigated the benefits of taking oleic acid along side fish oil supplements. They conducted a randomised parallel study on participants (n=43, all taking prednisone) who were allocated to either the placebo (group 1; soy oil), 3g/day fish oil (group 2; each capsule; 90mg EPA, 60mg DHA), or fish oil plus 6.8mg oleic acid (group 3; olive oil). Participants in the fish oil groups were expected to take 20 capsules per day. There was a significant improvement in groups 2 and 3 compared with group 1, for EMS, joint pain intensity (JPI), onset of fatigue, Ritchie's articular index, and hand grip strength after 24 weeks. Group 3 showed an enhanced improvement in EMS and JPI at 12 weeks and a greater improvement for the patient's global assessment of disease and functional capacity compared to group 2 at 24 weeks. Additionally only group 3 experienced a significant reduction in rheumatoid factor. This study suggests that MUFA's enhance the benefits of fish oil supplementation by increasing n-3 PUFA incorporation into phospho- lipid membranes and providing a more beneficial improvement in clinical and biochemical characteristics (Berbert *et al*., 2005). However this study design was not double blinded, and therefore may have initiated investigator or participant bias, and resulted in exaggerated differences between groups, perhaps with the exception of grip strength and laboratory markers.

Although there was no significant differences between the group's baseline characteristics, group 3 had the greatest number of females compared to male participants and greater amounts of prescribed drugs than group 1 and 2. Another limitation is that the placebo chosen (soy oil) contains n-6 PUFA which have been reported to be pro-inflammatory (Calder and Zurier, 2001); this may further exaggerate the differences between groups making them appear more significant.

A recent dual centre, double blind placebo-controlled randomised study conducted in Scotland (Galarraga *et al*., 2008) investigated the efficacy of cod liver oil (CLO) supplementation (10g/day; 150mg EPA, 70mg DHA, 80 µg vitamin A, 0.5µg vitamin D, 2.0 IU vitamin E) as a NSAID sparing agent. Participants (n=97) took either 10 1g capsules of CLO, or the same amount of air filled

capsules (placebo) daily. Of the participants who completed the study and were supplemented with CLO, 39% were able to reduce NSAID dosage by >30% compared to 10% in the placebo group. Unlike the previous studies they found no statistical improvement in clinical parameters between groups. Side effects such as nausea, vomiting, diarrhoea, flatulence, were experienced by 10 participants receiving CLO capsules, and 6 in the placebo group. A large number of participants (20/97) dropped out due to the size or inability to swallow such a vast amount of capsules. It must also be noted that, although this study design was double blinded, it was obvious that the placebo capsules were filled with air (Galarraga *et al.,* 2008), which may have resulted in outcome bias, skewed results and poor compliance. The study did not assess for the effect of the vitamin E, an antioxidant present in the CLO supplement, on disease activity. It has been reported that vitamin E supplementation may reduce the requirement for aspirin (an NSAID) (Rennie *et al.,* 2003), so its presence in the supplement may exaggerate the effects of the n-3 PUFA.

All of the above studies were randomised controlled trials (RCT) which are believed to be the ideal study design to determine the cause and effect of a treatment outcome, allowing for analysis of difference(Kendel, 2003). The sampling technique utilised by each study was not disclosed, only the sample population was reported for Berbert *et al*. (2005) and Galarraga *et al*. (2008), it is therefore unclear whether the chosen sample can be generalised to the rest of the population. Furthermore, with exception of Galarraga *et al*. (2008), the studies were conducted outside of the UK, which may reduce generalisability, if PUFA n-3 and n-6 intake and baseline characteristics are different across countries. Only Volker *et al.* (2000) controlled for baseline dietary n-6 PUFA intake (<10g/day), and therefore results from other studies may be biased and unreliable.

Clinical Nutrition and Dietetic Practice

The above studies show an improvement in clinical parameters such as EMS, however few have demonstrated an improvement in immune and biochemical parameters which may influence disease severity and progression(Calder and Zurier, 2001), and the efficacy of long term use has yet to be investigated. There are a number of limitations with the evidence in this area, the most prevalent and relevant to dietetic interventions are the complaint regarding the volume and number of fish oil capsules involved in the treatment groups (Galarraga *et al*., 2008). Calder and Zurier (2001) reviewed evidence from 1985 – 1995 and found a range of 1-7.1g of EPA and DHA, however the treatment doses of fish oils ranged from 10 capsules containing 1.5g EPA and 0.7g DHA (Galarraga *et al.,* 2008) to 12 capsules containing 2.04g EPA and 1.32g DHA (Tempel, 1990) in the above studies. Berbert *et al*. (2005) had the greatest number of capsules for their fish oil treatment (20 capsules/day), although only providing a total of 1.8g EPA, and 1.2g DHA. The number and size of the capsules required to initiate an anti inflammatory response and improve RA symptoms may be unacceptable to patients who are already taking a vast quantity of drugs. Additionally fish oil

capsules have been reported to give a fishy after taste, and are expensive to buy, and are not available on prescription (SIGN, 2000). A cheaper alternative may be to buy and drink ~10-20g bottled fish oil concentrate/day, however this is likely to be unpalatable (Simpoulos and Cleland, 2003). Current dietary recommendations for oily fish intake is 1-2 portions/week, and for secondary prevention of a heart attack the BDA recommend 2-3 portions of oily fish/week or 1g fish oil supplement/day (Tomas and Bishop, 2007). However the number of portions/week would greatly increase to reach the required doses to initiate an anti-inflammatory response. And therefore it may not be possible to achieve through diet alone. It should be noted that there are high levels of dioxins in fish oils, and greater amounts in cod liver oils, and intake should therefore not exceed 4 portions of oily fish per week in post reproductive women, boys and men, and if supplements are being taken, cod liver oils shouldn't be encouraged (SACN/COT, 2004).

NICE (2009) guidelines conclude that there is insufficient strong evidence to advocate dietary experimentation (including the use of fish oils), and recommend that people wishing to experiment should follow the principles of a Mediterranean diet (high in fruit and vegetables, fish, fibre and bread, n-3 PUFA and MUFA, and lower in red meat and SFA). A recent Cochrane review reported that a Mediterranean diet may reduce joint pain (Hagen *et al.* 2009). It has been reported that this diet is also cardio protective due to its low SFA, high MUFA and antioxidant content which is reported to reduce oxidative stress caused by ROS released during inflammation (Rennie *et al.,* 2003; Thomas and Bishop, 2007). This diet would therefore be beneficial for RA as the risk of CVD is increased (Rennie *at al*., 2003). SIGN (2000) recommend that the primary dietetic intervention is treatment of underweight and obesity, both of which are common with RA, this is important as obesity can increase weight bearing on arthritic joints and people with a lower BMI tend to have poor immune function (SIGN, 2000).

Recommendations for further investigation

Current studies have not investigated the long term safety, efficacy, acceptance and compliance of fish oil supplementation. This is an area that would be beneficial to dietetic practice. Simpoulos and Cleland (2003) suggest that an initial high dose of fish oils followed by a low maintenance dose may be a beneficial and more accepted approach to treatment of RA. Further research could therefore investigate the lowest dose of fish oils that still initiates symptom and inflammatory improvement in RA.

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