Editorial

Collateral Benefits of Fish Oil Therapy for Rheumatoid Arthritis

Recent scientific advances have improved our understanding of the cause and pathogenesis of rheumatoid arthritis (RA). Reports that monoclonal antibodies to the cytokine tumor necrosis factor-α (TNF-α) could significantly suppress symptoms and signs of RA will go down in history as one of the events that has changed the face of rheumatology. Regrettably, however, these agents are expensive and are not widely affordable for most health care systems. Further, despite their superiority over conventional disease modifying antirheumatic drugs (DMARD) in suppressing the RA disease process, the use of anti-TNF-α and other biologic agents are not without significant side-effects, notably chronic infections such as tuberculosis. Of course, a cure is not yet achievable with these drugs.

It is therefore understandable that patients continue untiringly to seek alternative therapies in managing their arthritis. "Natural remedies" and "folklore medicines," including the use of dietary supplements, are commonly practiced by patients with RA. Unfortunately, research in dietary supplementations as a form of treatment of RA has attracted variable opinions including criticisms and dismissals despite clear scientific evidence that some of these approaches are valid. It is therefore pleasing to be able revisit this topic.

Dietary supplementation with essential fatty acids (EFA) has been considered useful for RA. It is interesting to note that the prevalence of RA in Eskimos, who consume large amounts of oily fish rich in n-3 EFA, is low. EFA have unique roles as precursor molecules of chemical regulators, the so-called eicosanoids, including the prostaglandins (PG), leukotrienes (LT), and thromboxanes (TX). These compounds are synthesized and released by almost every tissue in the body, and participate in many biological functions, including the inflammatory and immune processes, as well as thrombosis and hemostasis. Most work has focussed on arachidonic acid (AA), the precursor of the 2-series PG and the 4-series LT that are responsible for the development of inflammatory responses. Altering the EFA content in the diet or administering different EFA in the form of supplements modifies the production of the various PG, LT, and TX[1]. For example, eicosapentaenoic acid (EPA) is metabolized to the less proinflammatory PG of the 3-series and LT of the 5-series. Previous studies have shown the intake of fish oil, which is rich in EPA and another EFA, docosahexaenoic acid (DHA), has antiinflammatory effects in the treatment of RA[2-6].

Although the antiinflammatory effects of dietary fish oil supplementation in RA have sometimes been dismissed as being modest with poor short term efficacy and probably inferior to the more commonly used nonsteroidal antiinflammatory drugs (NSAID), fish oil therapy has a distinct advantage of being very well tolerated by the majority of patients. Aside from occasional nausea, fish oil supplementation virtually has no major side effects, in particular it has not been associated with serious upper gastrointestinal (GI) complications that are commonly seen with NSAID therapy[7]. The introduction of specific inhibitors of the cyclooxygenase (COX)-2 isoenzyme was hailed as the answer to NSAID associated GI complications. Unfortunately, these drugs were later found to be associated with an increased risk of cardiovascular (CV) events[8], and doubts are being cast regarding their longterm use. Subsequently, other studies showed that an increased CV risk is not unique to COX-2 inhibitors but is also associated with NSAID[9]. This is particularly relevant for patients with RA who have twice the likelihood of CV death compared with the general population[10]. Thus, conventional antiinflammatory drugs are more than double-edged swords in the treatment of symptoms and signs of RA.

It will be most desirable if fish oil therapy is not just "gastrointestinally safe" but also confers protective effects on the CV system. Fish oil has been shown to have multiple beneficial vascular and antithrombotic effects[1], but this has not been thoroughly investigated in patients with RA. In this issue of The Journal[11], Cleland, et al attempted to

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examine the biochemical markers relevant to inflammatory symptoms and CV risk in RA patients advised to take an antiinflammatory dose of fish oil over a 3 year observation period.

In their open label study, the authors recruited patients with early RA requiring the use of DMARD (n = 73). Patients were given advice to take bottled fish oil with juice such that a daily intake of 4 to 4.5 g of EPA plus DHA was achieved. They were reviewed 3- to 6-weekly initially and subsequently 3-monthly when the disease was well controlled. Analyses were performed after patients had completed at least 3 years of treatment. Only data from patients who were compliant with the therapy and whose plasma EPA level was > 5% of total plasma phospholipid fatty acids throughout the study period were analyzed. These patients (Fish Oil group; n = 18) were compared with those who chose not to take fish oil (No Fish Oil group; n = 13) during the same study period. The authors found the index of AA availability for eicosanoid synthesis was 30% lower in platelets and 40% lower in peripheral blood mononuclear cells (PBMC) of the Fish Oil group compared to the No Fish Oil group. Correspondingly, there was a mean 35% decrease in platelet thromboxane B_2 production and 41% decrease in lipopolysaccharide stimulated PBMC synthesis of prostaglandin E_2 in the Fish Oil group compared to the No Fish Oil group. Favorable differences in plasma triglycerides, HDL cholesterol, and total cholesterol/HDL ratio were also seen in the Fish Oil group at 3 years but not the No Fish Oil group. Further, in accordance with previous studies, patients who consumed high doses of Fish Oil were able to lower or discontinue their use of NSAID. Interestingly, the proportion of patients in remission at 3 years was greater in the Fish Oil group than the No Fish Oil group (72% vs 31%).

This is an interesting study with much to commend. The two groups of subjects were balanced at baseline for disease activity and plasma phospholipid saturated and n-6 and n-3 fatty acids. There were also no statistical significant differences in the various lipid CV risk factors, although the Fish Oil group tended to have a lower plasma total choles- terol/HDL ratio. To confirm dietary compliance, which is a very important component of this study, the investigators used the plasma EPA level as an indicator, and only patients whose EPA per total plasma phospholipid fatty acid level was consistently above 5% were considered compliant and included in the final analysis. Previous studies have tended to use less reliable criteria to determine compliance. To evaluate the CV risk of the 2 groups of patients studied, the authors used a whole blood assay to measure eicosanoid synthesis, which is novel and objective. The most important feature of this study is its 3 year duration. This is the longest observation period to date of any Fish Oil study carried out in patients with RA.

There are weaknesses with this study. The number of patients in each group was small, although the long duration of study probably offsets this. The most important drawback is its open label, observational, non-randomized design. It is possible that those patients who "religiously" used fish oil during the study period were those who would look after their disease better and are more conscious of their health in general. The lower plasma total cholesterol/HDL ratio at baseline probably reflects this. Because of its open label design, results on the effects of fish oil treatment on RA disease symptoms and activity become less convincing. Nevertheless, their results are in general agreement with previous related reports. It is interesting that the disease remission rate at 3 years was lower in the Fish Oil group than the No Fish Oil group. Finally, no CV events were recorded in this study. This is obviously because of the small number of patients studied and this makes the reported lower AA availability for eicosanoid synthesis in platelets and PBMC less clinically relevant.

Notwithstanding the above pitfalls, this study represents one of the first attempts to evaluate the potential cardioprotective role of fish oil in RA. Previous studies have shown n-fatty acid supplementation is protective against cardiac deaths[12]. Hopefully, future controlled studies will confirm Cleland and colleagues' findings. Perhaps, one does not need to be an Eskimo to have less arthritis and cardiovascular thrombosis.

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