

Paying attention to the safety and efficacy of fish oil in treatment of knee osteoarthritis

We read with deep interest the article by Hill *et al*¹ who examined whether high-dose fish oil was superior to low-dose supplementation for symptomatic and structural outcomes in knee osteoarthritis (OA). This study suggested that The Western Ontario and McMaster Universities Arthritis Index (WOMAC) pain and function scores were improved in high-dose and low-dose fish oil groups compared with baseline, and high-dose groups had no additional benefit for people with symptomatic knee OA compared with low-dose groups. We really appreciate the work that has been done by the authors, but there are some worthwhile issues that need to be explored.

Since this study might encourage supplementation of fish oil (eicosapentaenoic acid (EPA)+docosahexaenoic acid (DHA)) in many patients with knee OA, we think, first, safety issues should be the object of particular scrutiny. Recent review² states that long-chain omega-3 fatty acids (EPA+DHA) intake dampens immunity and alters pathogen clearance and can result in reduced survival in animal models of infectious disease. Recent observations that high serum long-chain omega-3 fatty acids levels are associated with higher risk of prostate cancer and atrial fibrillation raise concern for adverse outcomes.^{2,3} In this study, the rates of gastrointestinal events were high in low-dose groups and high-dose groups (61.4% and 66.3%, respectively), as were rates of infection (65.3% and 71.3%, respectively), rates of cancer (8.9% and 11.9%, respectively) and rates of cardiovascular diseases (15.8% and 17.8%, respectively). Such complications are costly and worrisome adverse events, especially since 37% of American adults⁴ and 40% of Chinese women⁵ are now potential candidates for treatment. In addition, the authors stated that most people took about 1 mL of fish oil (approximately 0.3 g EPA+DHA) and the anti-inflammatory dose of fish oil was about 10 mL (≥ 2.7 g of EPA+DHA). Peanpadungrat⁶ selected 1.0 g or 2.0 g of fish oil once a day to study the efficacy and safety of fish oil in treatment of knee OA. We feel confused why the authors considered 4.5 g omega-3 fatty acids as high-dose fish oil and 0.45 g omega-3 fatty acids as low-dose fish oil. There is a real risk of consuming excess omega-3 fatty acids beyond 3 g/day, which is associated with adverse effects and, in extreme cases, negative health outcomes.² Thus, more explanation is expected. Also, the Food and Drug Administration (FDA) draft did not recommend fish oil supplements instead of eating fish, which is advice that may reflect the fact that randomised controlled trials of DHA and EPA or fish oil supplementation generally have been disappointing and that the ideal daily dose of DHA and EPA is unknown.⁷

The second relates to the efficacy of fish oil in actually decreasing WOMAC pain and increasing function scores. On the one hand, in consideration of the effects from fish oil treatment that do not depend entirely upon itself, the objective of the placebo control is to account for the placebo effect. The authors admitted that it led to difficulty of assessment due to lack of a control group. We agree with this. Another systematic review of 130 trials also reported that the placebo may have small benefits in studies with continuous subjective outcomes and for the treatment of pain.⁸ On the other hand, it should be

noted that analgesic drugs were used in this study, such as paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs), which were highly correlated with pain level.⁹ In addition, another review states that despite the overwhelming popularity of fish oil supplements and the assumption of benefit for patients with arthritis, there appears to be insufficient clinical evidence to justify use of fish oils in the treatment or prevention of OA.¹⁰ We, therefore, consider that the effect of fish oil on pain relief and function scores for knee OA might be overestimated.

We respect the great contributions of the authors and are looking forward to their response to these issues.

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