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 review[2] 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 adults[4] and 40% of Chinese women[5] 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). Peanpadungrat[6] 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.

Shu-Guang Gao,[1] Chao Zeng,[1] Jie Wei,[2,3] Yi-Lun Wang,[1] Guang-Hua Lei[1]

[1]Department of Orthopaedics, Xiangya Hospital, Central South University, Changsha, Hunan Province, China
[2]Health Management Center, Xiangya Hospital, Central South University, Changsha, Hunan Province, China
[3]Department of Epidemiology and Health Statistics, School of Public Health, Central South University, Changsha, Hunan Province, China

Correspondence to Professor Guang-Hua Lei, Department of Orthopaedics, Xiangya Hospital, Central South University, Xiangya Road, Changsha, Hunan Province, 410008, China; lgh9640@sina.cn

Contributors S-GG, concept, writing; CZ, JW, Y-LW: writing; G-HL, concept, revising.

Funding China (grant numbers 81201420, 81272034, 81472130).

Competing interests None declared.

Provenance and peer review Not commissioned; internally peer reviewed.

To cite Gao S-G, Zeng C, Wei J, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year] doi:10.1136/annrheumdis-2015-208880

Received 9 November 2015
Accepted 10 November 2015

Ann Rheum Dis 2015;**0**:1. doi:10.1136/annrheumdis-2015-208880

REFERENCES

1 Hill CL, March LM, Aitken D, *et al*. Fish oil in knee osteoarthritis: a randomised clinical trial of low dose versus high dose. *Ann Rheum Dis* 2015. Published Online First 9 Sept 2015. doi: 10.1136/annrheumdis-2014-207169
2 Fenton JI, Hord NG, Ghosh S, *et al*. Immunomodulation by dietary long chain omega-3 fatty acids and the potential for adverse health outcomes. *Prostaglandins Leukot Essent Fatty Acids* 2013;89:379–90.
3 Brasky TM, Darke AK, Song X, *et al*. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *J Natl Cancer Inst* 2013;105:1132–41.
4 Dillon CF, Rasch EK, Gu Q, *et al*. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third National Health and Nutrition Examination Survey 1991–94. *J Rheumatol* 2006;33:2271–9.
5 Zhang Y, Xu L, Nevitt MC, *et al*. Comparison of the prevalence of knee osteoarthritis between the elderly Chinese population in Beijing and whites in the United States: the Beijing Osteoarthritis Study. *Arthritis Rheum* 2001;44:2065–71.
6 Peanpadungrat P. Efficacy and safety of fish oil in treatment of knee osteoarthritis. *J Med Assoc Thai* 2015;98(Suppl 3):S110–14.
7 Wenstrom KD. The FDA's new advice on fish: it's complicated. *Am J Obstet Gynecol* 2014;211:475–8.e1.
8 Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001;344:1594–602.
9 Day RO, Graham GG. Non-steroidal anti-inflammatory drugs (NSAIDs). *BMJ* 2013;346:f3195.
10 Boe C, Vangsness CT. Fish oil and osteoarthritis: current evidence. *Am J Orthop (Belle Mead NJ)* 2015;44:302–5.