

Dietary fatty acids for the treatment of OA, including fish oil

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Osteoarthritis (OA) is the most common musculoskeletal disorder and its prevalence is increasing.¹ Non-surgical treatments are often frustratingly ineffective and while some medical treatments are modestly efficacious, none are approved that delay the course of disease. The failure of medical treatments for OA of both the hip and the knee is a primary underlying reason for the rapidly increasing rates of knee and hip replacements in developed countries. New efficacious therapies that might alleviate pain or delay the structural progression of this disease are badly needed.

One promising major approach for treatment of OA is abrogation of the inflammatory response within the joint. Increasingly, OA is regarded as an inflammatory disease² even though the degree of inflammation varies and is often modest. MRI studies have shown that the synovitis that commonly accompanies disease in the knees and hands contributes to disease progression, including cartilage loss. MRI-based studies have shown that synovitis is likely to be a major cause of joint pain. In fact, at least two of the known efficacious treatments for OA target inflammation within the joint: non-steroidal anti-inflammatory drugs and intra-articular corticosteroids. The latter are highly effective in relieving joint pain over a short term in many patients. We have recently shown that intra-articular steroids relieve pain in part by reducing synovitis within the knee.³ Ongoing studies are evaluating whether reduction in synovitis can not only reduce pain but also stanch the progression of structural disease. It stands to reason that any treatment targeting inflammation within the joint might be expected to reduce pain and maybe even delay structural

deterioration in the diseased joint. It is with this background that Hill and colleagues⁴ conducted a randomised trial of high-dose (4.5 g) versus low-dose (0.45 g) omega 3 fatty acids in 202 patients with knee OA followed up to 24 months. The low-dose compound provided a dose equivalent to 1.5 standard 1 g fish oil capsules daily. The primary structural outcome, quantified cartilage volume on MRI, did not show any significant differences in change between groups. The surprising finding was in the pain outcomes. As is frequent in OA trials, pain diminished in both groups but it decreased *more* in the group on *low-dose* fish oil, with between-group results statistically significant at 18 and 24 months for both pain and function. How can one explain these unexpected and paradoxical results?

First, is it possible that higher doses of fish oil actually have a paradoxical effect causing worsening of symptoms? In rheumatoid arthritis (RA), higher doses of fish oil have been associated with a greater efficacy with respect to pain reduction in the number of tender joints and morning stiffness⁵ and while some dietary factors such as vitamin E have been found to have paradoxical negative findings when dose is increased, this has not been reported for essential fatty acids and would be unlikely given the increasing anti-inflammatory effect of higher doses.

Second, the low-dose fish oil did not contain only fish oil but rather was enriched with oleic acid, also classified as a monounsaturated omega-9 fatty acid. Hill and colleagues avoided olive oil as a comparator since olive oil contains polyphenols which have been shown to have antioxidant effects and probably also anti-inflammatory effects.⁶ Instead, they used a form of Sunola oil highly enriched with oleic acid. One important question that was unanticipated by this or other studies is whether oleic acid, even though it does not contain polyphenols, might itself have anti-inflammatory effects. There are two routes by which oleic acid may suppress inflammation. In obese persons, free fatty acid clearance is compromised. Saturated free fatty acids, especially palmitic acid, induce toll-like receptor 4 (TLR-4) signalling and extracellular matrix degradation. There is evidence from in vitro systems

that when oleic acid is present in large concentrations relative to palmitic acid, oleic acid predominance suppresses insulin resistance and inflammation in muscle cells⁷ and that in colonic cells,⁸ oleic acid can counteract the proinflammatory effect of arachidonic acid. In vivo effects are unknown. Second, while the importance of adaptive immunity in OA is unclear, oleic acid in vitro prevents adherence of cytotoxic T lymphocytes to major histocompatibility complex (MHC) class I targets,⁹ preventing at least one mechanism of cytotoxicity. Thus, while there is a paucity of in vivo data on effects of large doses of oleic acid, there is suggestive evidence that it may have some anti-inflammatory effects.

In RA trials, fish oil reduced symptoms within 3 months compared with placebo.¹⁰ Even though adherence to treatment was good and an intent-to-treat analysis with imputed missing data was carried out, the difference between the low-dose and high-dose fatty acid groups in the trial by Hill *et al* did not reach statistical significance until 18 months after the start of the trial ($p < 0.05$), raising questions about the validity of the finding.

Lastly, statistical significance does not necessarily equate to truth. Given the 18-month result of significance ($p < 0.05$) between the groups, there is a $< 2\frac{1}{2}\%$ chance that the two treatments were equivalent with respect to pain reduction. Finding a significant result when there is in fact no real difference between treatments is a type I error which is possible here, although the 24-month result ($p < 0.01$) makes a type I error less likely.

Ultimately, the well-done study by Hill *et al* has provided valuable new data on the treatment of OA. It is not clear how to interpret these data but the most likely explanation is that oleic acid itself has a positive effect on knee pain (perhaps through anti-inflammatory effects) or that the difference between high-dose fish oil and low-dose fish oil was a type I error. Notably, we could not find data to support the alternative concept of 'too much of a good thing' with respect to omega-3 fatty acid dose and inflammation.

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