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OMEGA-3 FATTY ACIDS AND HEALTHY JOINTS

The use of fish oils to treat or "cure" "rheumatism," as painful conditions of the joints used to be known, was long practised by the Vikings who rubbed cod liver oil on their joints to relieve soreness.[1] A case report of its success in easing rheumatism appeared in the U.K. in 1782 and by 1822 the medical profession had recognized the curative properties of cod liver oil. However, cod liver oil fell into disuse, except for its ability to cure rickets in children which was attributed to its digestibility.[1] A resurgence of interest in the effectiveness of marine oils rich in long-chain omega-3 polyunsaturated fatty acids (omega-3 PUFAs) in inflammatory diseases and joint disorders has led to several clinical trials in which the consumption of omega-3 PUFAs has been associated the alleviation of symptoms and other medical benefits.

Rheumatoid arthritis[2] (RA) is a chronic and progressive autoimmune disease where inflammation affects many tissues and organs, principally the flexible joints. It may occur in conjunction with certain infections, psoriasis, systemic lupus erythematosus or other connective tissue diseases. Typical symptoms include persistent pain, swelling, redness and stiffness of the joints, especially in the morning. Typically, it affects the joints in the hands, wrists and feet. The inflammatory process attacks the tissue surrounding the joint causing it to thicken. As the disease progresses, inflammation destroys the cartilage and erodes the bone. The disease affects approximately 1.5 million people in the U.S., occurring two to three times more frequently in women than men. Although there is no cure for RA, several interventions can ease many of its symptoms, slow disease progression and reduce the medications required. Management of RA currently relies mainly on synthetic and biologic drugs.[3]

Early observations among populations in the Arctic reported an unusually low number of cases, which eventually led to the link between low rates of immune-based diseases with a diet high in marine foods.[4,5] More recent studies have confirmed that diets low in fish or omega-3 PUFAs carry a significantly higher risk of RA.[6-8] Further, RA patients who consumed a diet low in arachidonic acid, an omega-6 PUFA, experienced a reduction in their symptoms beyond that achieved with fish oil supplementation alone.[9] The shift in Western diets away from omega-3 PUFAs toward much higher intakes of omega-6 PUFAs from vegetable oils would be expected to exacerbate the risk of RA, as has been suggested.[10,11] Other modifiable habits associated with a greater risk of RA are smoking[12] and possibly high caffeine and red meat consumption,[13] while alcohol intake[14,15] and a Mediterranean diet may reduce the risk.[16] Fish and fish oil are most strongly linked to a lower risk of RA.[17]

Epidemiological observations and the anti-inflammatory properties of fish oils rich in omega-3 PUFAs led to trials with fish oil in RA patients.[18,19] Clinical outcomes included significant reductions in the number of tender joints, the duration of morning stiffness and a delayed onset of fatigue, improvements that deteriorated after treatment ceased.[19,20] A meta-analysis of 16 studies reported significant reductions in pain measures after three to four months' treatment.[21] The review noted that outcomes improved with omega-3 PUFA consumption for five months or longer. Investigators noted, however, that relatively large doses of omega-3 PUFAs (3 to 6 g/day)[22] are necessary to achieve clinical improvements, which may require two to three months to develop.[23]

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An additional benefit of omega-3 PUFA treatment in RA is the elimination or reduction of the amount of nonsteroidal anti-inflammatory drugs (NSAIDs) and other disease-modifying medications needed to control symptoms.[24-26] When added to a drug protocol, fish oil enhanced the rate of disease remission and the effectiveness of the drug treatments.[26] NSAIDs (e.g., aspirin, ibuprofen) are widely used to relieve pain and have been associated with adverse gastrointestinal, renal and cardiovascular side effects and may be poorly tolerated.[27,28] Acetaminophen (paracetamol) may be a preferable pain-reliever and was more effective in suppressing prostaglandin E_2 synthesis when combined with fish oil.[29,30] Thus, omega-3 PUFAs can be a useful and effective adjunct to drug therapy.

The rapid growth in understanding the mechanisms of immune-based diseases and the influence of fatty acids in producing or inhibiting inflammatory responses[31] prompted investigation into the effects of omega-3 PUFAs on inflammatory mediators in RA. As expected, the consumption of omega-3 PUFAs was accompanied by a reduction in leukotriene B_4,[18,20] interleukin-1β,[32] TNF-α,[33] thromboxane B_2[34] and prostaglandin E_2,[34] all proinflammatory mediators. These effects are due in part to the production of less inflammatory prostaglandins and leukotrienes derived from EPA.[35] Moreover, omega-3 PUFAs stimulate the production of resolvins, derivatives of EPA and DHA with potent anti-inflammatory and pro-resolving properties.[36] Resolvins were also reported to decrease inflammation-associated pain in an experimental model of RA[37] and are emerging as potent therapeutic agents in RA.[36]

There are other benefits to RA patients who consume omega-3 PUFAs with other medications. Of particular importance is a significant reduction in cardiovascular risk, which is doubled in RA.[34,38] Hypertension is higher among RA patients than those without RA[39] and may be modestly reduced with the consumption of omega-3 PUFAs.[40,41] Reduced kidney function that may develop in RA patients is also improved with greater omega-3 PUFA intakes.[42,43] Other cardiovascular risk factors are also affected by the consumption of omega-3 PUFAs, including the reduction of blood triglycerides, increased arterial compliance, attenuated vascular inflammation and others.

Deterioration in bone health is another consequence of RA and some of the drugs used to treat it. This may present as subclinical inflammation of the synovial membrane, bone edema, cartilage thinning or other damage observed using magnetic resonance imaging.[44] Other risks include bone erosion, vertebral and other bone fractures, low bone mineral density and osteoporosis.[45-47] Higher intakes of omega-3 PUFAs have been associated with higher lumbar spine bone mineral density in older adults, lower risk of hip fractures in postmenopausal women and several bone-protective effects at the cellular level.[48-50] Resolvin E1 was shown to protect against bone loss in an experimental model of periodontitis.

The other common joint disease is osteoarthritis (OA), a degenerative condition involving erosion and loss of cartilage at the ends of the bones, bone remodeling and inflammation of the synovial membrane. It is the most common type of arthritis in the U.S., affecting approximately 37% of adults above the age of 60 years.[51] Risk of developing OA is significantly higher in women, with advancing age and the obese.[52] It is painful and can be debilitating and thus, is a frequent reason for knee or hip replacement.[53]

Several studies on the effects of omega-3 PUFAs in animals with OA[52] demonstrated significantly reduced symptoms, but studies in humans and human tissues are only now emerging. In explants of bovine cartilage treated with the proinflammatory cytokine IL-1β, the addition of omega-3 PUFAs to the culture medium led to a significant decrease in the release of a structural substance from the cartilage, suggesting reduced tissue breakdown.[54] This effect was attributed to the anti-inflammatory effect of the omega-3 PUFAs. A recent study in OA patients focused on synovitis, inflammation of the synovial membrane lining the capsule surrounding the joint. Synovitis occurs relatively early in OA and may predict progression of the disease.[55] The researchers examined the association between plasma omega-6 and omega-3 PUFAs and synovitis and reported that higher levels of arachidonic acid (an omega-6 PUFA) were associated with more synovitis.[56] Higher levels of total omega-3 PUFAs or DHA, but not EPA (long-chain omega-3 PUFAs), were unrelated to synovitis, but were associated with less cartilage loss in the patellofemoral region (back of the knee next to the thigh bone). These observations suggest that available arachidonic acid derived from linoleic acid, the primary dietary PUFA, might increase the odds of developing OA,[57] and that omega-3 PUFAs may reduce synovitis and cartilage loss in the knee. The implications of this study are consistent with observations in animals and laboratory studies.[58,59]

In summary, the consumption of large amounts of omega-3 PUFAs is associated with extensive improvements in the symptoms of RA, a reduced need for medications and significantly lower risks of cardiovascular, hypertensive, renal and bone diseases associated with the disease. Emerging evidence suggests that omega-3 PUFAs may be useful in OA, but data are too sparse for conclusions.

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