

Annals of the Rheumatic Diseases

Leaders

Nutrition: risk factors for osteoarthritis

Questions about the role of diet in the prevention and treatment of their joint disorder may be among the most frequent posed by patients with osteoarthritis (OA). Interestingly, while there are thousands of lay publications recommending various arthritis diets, physicians have little information to offer based on scientific studies.¹ Arguably, in no other aspect of rheumatology is public and medical interest so discrepant. Indeed, the traditional medical approach has been to counsel patients that, other than diets promoting weight loss, scientific research has produced no evidence to suggest that any particular nutritional intervention might be helpful for OA.² In fact, studies do suggest pathways through which nutritional factors might influence the natural history of OA.

Diet and obesity

Overweight people are at considerably increased risk for the development of OA in their knees, and may also be more susceptible to both hip and hand joint involvement.³ As overweight people do not necessarily have increased load across their hand joints, investigators have wondered for decades whether systemic factors, such as dietary factors or other metabolic consequences of obesity, may mediate some of this association. Indeed, early laboratory studies using strains of mice and rats seemed to suggest an interaction between body weight, genetic factors, and diet, although attempts to demonstrate a direct effect of dietary fat intake proved inconclusive.^{4,5} Irrespective of the mechanism, it seems reasonable to infer that weight reduction, through dietary or other means, may reduce a person's risk for the development or progression of OA. Observational data from the Framingham OA Study support this notion and suggest that weight loss of approximately 5 kg will reduce a person's risk for the development of knee OA over the subsequent 10 years by 50%.⁶

Unfortunately, dietary intervention for obesity in uncontrolled environments is often costly, unpleasant, and frequently ineffective, particularly in the long term.⁷ Furthermore, it is increasingly apparent from studies of the genetics of obesity, and the biology and physiology of weight regulation, that obesity is a disorder with many more facets than the simplistic equation relating energy output with expenditure.^{8,9} In light of these facts, and the numerous adverse medical and psychological effects associated with dieting, many investigators now believe that weight loss through dietary intervention alone is difficult to justify.¹⁰

Vitamins C and E

ANTIOXIDANT EFFECTS

A variety of reactive oxygen species (ROS) (chemical species with unpaired electrons) are formed continuously in tissues by endogenous and some exogenous mechanisms.¹¹ For example, it has been estimated that 1–2% of all electrons that travel down the mitochondrial respiratory chain leak, forming a superoxide anion (O_2^-).¹² Other endogenous sources include release by phagocytes during the oxidative burst, generation by mixed function oxidase enzymes, and in hypoxia-reperfusion events.¹³ ROS are capable of causing damage to many macromolecules including cell membranes, lipoproteins, proteins, and DNA.¹⁴ Because these ROS are identical to those generated by irradiation of H_2O , 'living' has been likened to being continuously irradiated.¹¹ ROS mediated damage accumulates with age and has been implicated in the pathophysiology of a number of common age related conditions such as cataract,¹⁵ coronary artery disease,¹⁶ and certain forms of cancer.¹⁷

OA similarly can be regarded as a prototypical age related 'degenerative' disease. Furthermore, there is evidence that cells within joints produce ROS, and that oxidative damage is physiologically important.¹⁸ In laboratory studies, animal and human chondrocytes have been found to be potent sources of ROS.^{18,19} Hydrogen peroxide production has been demonstrated in aged human chondrocytes after exposure to interleukin 1 or tumour necrosis factor α , and has been observed in live cartilage tissue.²⁰ Superoxide anions have been shown to adversely affect collagen structure and integrity in vitro, and seem to be responsible, in vivo, for depolymerisation of synovial fluid hyaluronate.^{19,21,22}

In fact, the human body has extensive and multi-layered antioxidant defence systems.¹¹ Intracellular defence is provided primarily by antioxidant enzymes including superoxide dismutase, catalase, and peroxidases. In addition to these enzymes, there are a number of small molecule antioxidants that play an important part, particularly in the extracellular space, where antioxidant enzymes are sparse.²³ These include the micronutrients α tocopherol (vitamin E), β carotene (a vitamin A precursor), other carotenoids, and ascorbate (vitamin C), whose blood concentrations are primarily determined by dietary intake. The concept that micronutrient antioxidants might provide further defence against tissue injury when intracellular enzymes are overwhelmed, has led to the

hypothesis that high dietary intake of these micronutrients might protect against age related disorders. Indeed, higher intake of dietary antioxidants seems beneficial in respect of outcomes such as cataract extraction and coronary artery disease.²⁴⁻²⁷

We investigated the association of reported dietary intake of antioxidant micronutrients among participants followed up longitudinally in the Framingham Knee OA Cohort Study.²⁸ Participants had knee *x* rays taken at examinations 18 (1983-5) and 22 (1992-3). Nutrient intake, including supplement use, was calculated from dietary habits reported at examination 20 in a food frequency questionnaire. We looked specifically to see if higher intakes of vitamin C, vitamin E, and β carotene, compared with a panel of non-antioxidant 'control' micronutrients, were associated with reduced incidence and reduced progression of knee OA. We found no significant association of incident radiographic knee OA with any micronutrient (for example, adjusted odds ratio (OR) for highest *v* lowest tertile of vitamin C intake=1.11, 95% confidence limits 0.56, 2.18). On the other hand, for progression of radiographic knee OA, we found a threefold reduction in risk for those in the middle and highest tertiles of vitamin C intake (adjusted OR for highest *v* lowest tertile=0.3; 95% confidence limits 0.1, 0.6). Those in the highest tertile for vitamin C intake also had reduced risk of developing knee pain during the course of the study (aOR=0.3; 0.1, 0.8). Reduction in risk of progression was also seen for β carotene (aOR=0.4; 0.2, 0.9) and vitamin E (aOR=0.7; 0.3, 1.6) but was less consistent, in that the β carotene association diminished substantially after adjustment for vitamin C, and the vitamin E effect was seen only in men.

Thus, while results from the Framingham Study do not support the hypothesis that diets high in antioxidant micronutrients reduce the risk of incident knee OA, they do raise a question about whether antioxidants might benefit people with established disease. Such a situation seems pathophysiologically plausible given the greater potential for hypoxia-reperfusion and low grade inflammation in osteoarthritic joints. Intriguingly, intra-articular superoxide dismutase (orgotein), an inhibitor of superoxide radicals, has been used for years in veterinary medicine in the treatment of equine osteoarthropathy. Orgotein has also been tested in placebo controlled clinical trials as a treatment for OA in humans, and has been found to be efficacious in comparison to placebo.^{29,30}

Benefit from vitamin E treatment has been suggested in several small studies of human OA,³¹⁻³⁴ of which the most rigorous was a company sponsored six week double blind placebo controlled trial of 400 mg α tocopherol (vitamin E) in 56 OA patients in Germany.³⁵ Vitamin E treated patients experienced greater improvement in every efficacy measure including pain at rest (69% better with vitamin E *v* 34% better with placebo, $p<0.05$), pain on movement (62% better with vitamin E *v* 27% with placebo, $p<0.01$), and use of analgesics (52% less with vitamin E; 24% less with placebo, $p<0.01$).

There are, however, a number of problems that add complexity to the study of antioxidants in OA. One fundamental issue is that there is no currently available test with which to objectively measure oxidant activity within joints. Inference about the pathophysiological effectiveness of these agents, therefore, must currently remain speculative, and it remains possible that any observed benefit might actually be produced through some other pathway. Secondly, comparatively little is known about the tissue distributions and bio-availability of antioxidant molecules within joints. For example, it is not clear whether lipophilic molecules (such as vitamin E or β carotene) might be

available at sites of cartilage damage. If lipophilic molecules have limited access to tissue compartments at which damage is manifest, hydrophilic antioxidants (such as vitamin C) may be the only agents likely to benefit the disorder.

NON-ANTIOXIDANT EFFECTS OF VITAMIN C AND VITAMIN E

In addition to being an antioxidant, vitamin C performs biochemical functions that might be clinically important in OA. Firstly, through the vitamin C dependent enzyme lysylhydroxylase, vitamin C is required for the post-translational hydroxylation of specific prolyl and lysyl residues in procollagen, a modification essential for stabilisation of the mature collagen fibril.^{36,37} Also, by acting as a carrier of sulphate groups, vitamin C seems to be required for glycosaminoglycan synthesis.³⁸ Peterkofsky, in studies of scorbutic guinea pigs, observed decreased synthesis of collagen and proteoglycan in cartilage, and also high values of the IGF binding proteins that inhibit the anabolic effects of IGF1.³⁹ Thus, vitamin C may also have effects on growth factors through pathways that remain to be elucidated.

Schwartz and Adamy, using chondrocyte cultures from normal and osteoarthritic tissues found a decreased level of active proteinase in the presence of ascorbic acid and found further that sulphated proteoglycan biosynthesis, a presumed measure of repair, was significantly increased in cartilage in the presence of ascorbic acid.³⁸ Sandell and Daniel studying adult bovine articular chondrocytes found an increase in type II procollagen mRNA, the precursor to type II collagen when chondrocytes were incubated with ascorbic acid.⁴⁰

Vitamin E blocks the formation of arachidonic acid from phospholipids and inhibits lipoxygenase activity, although it has little effect on cyclooxygenase.⁴² This suggests that vitamin E could affect the modest synovial inflammation that sometimes accompanies OA and may account for symptoms. Indeed, the positive effect of vitamin E seen in the short-term arthritis trials could be explained by an effect on inflammation.

VITAMIN C IN ANIMAL MODELS OF OA

Schwartz and Leveille induced OA in guinea pigs and treated them before surgery with either a high (150 mg/day) or low (2.4 mg/day) dose of vitamin C.⁴² Guinea pigs treated with the higher dose of vitamin C (which would correspond to vitamin C in humans of at least 500 mg/day) showed, 'consistently less severe joint damage than animals on the low level of the vitamin'. For example, cartilage fibrillation, structural changes in the joint and eburnation were significantly less frequent in the animals treated with the high dose of vitamin C. Osteophyte formation was less frequent in one of two operated groups. In a later experiment, Meacock and colleagues produced OA in guinea pigs using a medial meniscectomy and added ascorbic acid to the drinking water of one experimental group, whereas the other group had feed that contained less ascorbic acid.⁴³ They reported, 'Extra ascorbic acid appeared to have some protective effect ($p=0.008$) on the development of spontaneous lesions.... The effect of ascorbic acid appeared less on surgically induced osteoarthritis than on the development of the contralateral spontaneous osteoarthritis'.

Vitamin D and OA

ROLE OF BONE IN OA

Since its earliest descriptions, it has been recognised that pathophysiological changes in periarticular bone are an integral part of the process known as OA.⁴⁴⁻⁵⁰ These changes in subchondral bone may have adverse effects as a

result of decreased compliance and shock absorbing capacity⁵¹ or impaired reparative response,⁵² or may be beneficial in terms of stabilising an osteoarthritic joint⁵³ or containing the disease process.⁵⁴ It has also been suggested that bone mineral density may influence the skeletal expression of the disease.⁵⁵ The idea that the nature of bony response in OA may determine outcome has been further advanced by the recent demonstration that patients with bone scan abnormalities adjacent to an osteoarthritic knee have a higher rate of progression than those without such changes.⁵⁶ Normal bone metabolism is contingent on the presence of vitamin D, a compound that is derived largely from the diet or from cutaneous exposure to ultraviolet light. Suboptimal vitamin D concentrations may have adverse effects on calcium metabolism, osteoblast activity, matrix ossification, and bone density.^{57,58} Low tissue concentrations of vitamin D may, therefore, impair the ability of bone to respond optimally to pathophysiological processes in OA, and predispose to disease progression.

EFFECTS OF VITAMIN D ON CHONDROCYTES

Another mechanism through which vitamin D might influence OA is by direct effect on articular chondrocytes. During skeletal growth, vitamin D regulates the transition from growth plate cartilage to bone. It has recently become apparent that hypertrophic chondrocytes in osteoarthritic cartilage can redevelop vitamin D receptors.⁵⁹ These chondrocytes synthesise an excess amount of type X collagen and may also be responsible for calcification of matrix and for increased production and activation of collagenase and other metalloproteinases.⁶⁰ Hypertrophic chondrocytes are also capable of inducing angiogenesis, which might play a part in OA. Recently, Gerstenfeld *et al* reported that adult chicken hyaline cartilage responded to 1-25 dihydroxy vitamin D by acquiring an adherent, polygonal morphology and increasing production of type I, type II, type IX, and especially, type X collagen.⁶¹ Also, vitamin D has been shown to stimulate synthesis of proteoglycan by mature articular chondrocytes in tissue.⁶¹ Thus, articular cartilage, especially cartilage from OA, seems to be sensitive to the effects of vitamin D, although its exact effects on matrix synthesis and degradation are unclear.

STUDIES OF VITAMIN D IN HUMAN OA

We investigated the association of vitamin D status on the incidence and progression of knee OA in the Framingham OA Cohort Study. Participants had knee x rays taken at examinations 18 (1983-5) and 22 (1992-3).⁶² We used two measures of vitamin D status at exam 20; dietary intake, estimated using a food frequency questionnaire, and serum 25 hydroxy-vitamin D. As with the antioxidant study, we found no effect of vitamin D status on the risk of incident knee OA (for example, OR for lowest *v* highest tertile of dietary vitamin D intake=1.02, 95% confidence limits=0.45, 1.87). Risk of progression, however, increased threefold to fourfold for participants in the middle and lower tertiles of both vitamin D intake (OR for lowest *v* highest tertile=4.0, 95% confidence limits=1.4, 11.6) and serum concentration (OR=2.9, 95% confidence limits=1.0, 8.2). We concluded that low serum concentration, and low intake, of vitamin D each seem to be associated with an increase in the risk of knee OA progression.

Conclusion

It is clear that nutritional factors can be hypothesised to influence the course of OA through a wide variety of mechanisms. Preliminary results from numerous laboratory and observational studies seem to support this possibility. On the other hand, studies of such factors in

relation to a slowly progressive chronic disease are limited by many considerations such as the potential for confounding, problems with outcome definitions, absence of indicators of disease activity, imprecision and misclassification in measurement of dietary variables, and by many other factors. While providing no definitive answers, they underscore the importance of nutrition as an important area for further research and pull the subject of 'diet and arthritis' into the domain of scientific research.

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