

Nutritional Factors and Osteoarthritis: A review article

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ABSTRACT: Osteoarthritis (OA) is the most common disease according to TNS Arogya survey 2007. Although OA was previously thought to be a progressive degenerative disorder, it is now known that spontaneous arrest or reversal of disease can occur. Conventional medications are often effective for symptomatic relief but they can also cause significant side effects and do not slow the progression of disease. Though the role of nutritional factors in OA has been suggested as early as 700 BC, it was first established in the 1960s. Several nutritional factors are helpful in relieving the symptoms of OA and they might positively affect the progression of the disease without any side effects. Preliminary evidences suggest several of these may have a role in influencing the course of OA. Studies have proven the role of these factors and experiment based results have established their therapeutic role. Research is ongoing on the beneficial properties of plant derived extracts for OA and nutraceuticals industries are accordingly making firm contribution to this sector. This article focuses the role of nutrients to slow down the progression of OA and their future aspects.

KEY WORDS: Osteoarthritis; Dietary factors; Nutrition; Review

INTRODUCTION

Osteoarthritis (OA) is one of the most prevalent and disabling chronic disease affecting the elderly. The current concept holds that osteoarthritis involves the entire joint organ, including the subchondral bone, menisci, ligaments, periarticular muscle, capsule, and synovium¹. Its most prominent feature is the progressive destruction of articular cartilage which results in impaired joint motion, severe pain, structural and functional failure of synovial joints². Broadly OA can be subdivided in to two types: Primary OA and Secondary OA. Idiopathic (Primary) OA is most common form of disease and no predisposing factor is apparent. Secondary OA is pathologically indistinguishable from idiopathic OA but attributable to an underlying cause like

accidental injury to joints, inflammatory disease, healed infections of the joints, sports injuries, obesity, avascular necrosis of head of femur, congenital disorder, etc. Onset and progression of disease depends on various factors like obesity, joint injury, metabolic diseases, bone and joint malformation, genetic factors and nutritional factors³⁻⁶. Management of OA includes conventional pharmacological treatment of OA consisting primarily of non steroidal anti inflammatory drugs (NSAID's) and physiotherapy. While these medications often relieve symptoms, they are not ideal therapeutic agents. NSAIDs in particular, can cause serious side effects including peptic ulcer and hepatic or renal failure. Neither of these classes of medications prevents or delays the progression of OA^{7,8}.

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The role of nutrition and nutritional supplements in the development and progression of osteoarthritis is now a topic of considerable public, industrial, and academic interest. A number of substances that occur naturally in the body may have value for the prevention and treatment of OA. Some of these compounds have been shown to provide symptomatic relief and preliminary evidence suggests that some of them positively affect the progression of disease and

can be used to prevent the degradation, or enhance the repair of the joint cartilage. This review focuses a role of nutritional factors or nutritional supplements in the management of osteoarthritis.

HISTORICAL BACKGROUND

Correlation of OA and diet is as old as 700 BC, when use of millets was restricted for patients of joint pain when the cause was not known.

Year	Conclusions
1960's	Association of dietary factors or other consequences of obesity with OA and role of niacinamide is identified in OA
1970's	Role of vitamin C, E and Zn is identified but not proven.
1980's	Role of Obesity, Folic acid, Vitamin C, D, E, β-carotene, Zn, Se, Role of ROS known.
1990's	Role of n-3 fatty acid, ROS, Leutin and Zeaxanthin and weight reduction in OA.
2000's	Nutraceutical application of Conjugated linoleic acid (CLA), Poly unsaturated fatty acid (PUFA), Flavanoid
2005	Dietary supplementation programs and nutraceuticals used in conjunction with nonsteroidal, anti-inflammatory drugs may offer significant benefits to patients with OA. Significantly positive correlation was found between synovial fluid <i>Se-Cu</i> values in patients with RA but not with OA
2006	Weight loss has improved the physical function of the OA patients.
2007-2008	Recent studies assessed oxidative stress and antioxidant status in OA. They suggest higher oxygen free radical provides support to oxidative stress in OA. Micronutrient might mediate the OA process by blocking oxidative damage. Role of plant extracts and Nutraceutical was found against OA.

BIOLOGICAL EVIDENCE OF ROLE OF NUTRITIONAL FACTORS IN BONE PHYSIOLOGY

The bone is a living tissue from which substances are constantly being removed and replaced. Bone is made up of a protein matrix, on which hydroxyapatite (a crystalline structure made up of calcium and phosphorus) is deposited. Magnesium, zinc and fluoride are also deposited in the protein matrix, although calcium is the most abundant mineral in bone. Bone formation is laid down in two phases: *special organic matrix is laid down by Osteoblasts and then mineralization or calcification takes place.* Bone is continuously being remodeled, that is old bone tissue is replaced by new. Bone formation and bone resorption (replacement of old bone tissue) take place throughout life. Bone formation and bone resorption are influenced by a variety of factors including diet and physical activity. Bone formation is greater than bone

resorption until the age of 30-35 years, when peak bone mass is reached, the net effect being an increase in bone mass. After this bone resorption occurs at a faster rate than bone formation. The consequence of this is a gradual fall in bone mass with aging; bone minerals and proteins are lost slightly more quickly as from the age of about 35 years than they are replaced. The amount of calcium in bone gradually decreases. In women, bone loss is accelerated following the menopause, particularly during the first 5 years. This is because the hormone estrogen (production of which ceases after the menopause) protects bone, and bone formation and loss is negatively influenced by such hormones.

PATHOPHYSIOLOGY OF OSTEOARTHRITIS

Pathology of OA starts from fibrillation and ends at sclerosis as shown in **Figure 1**.

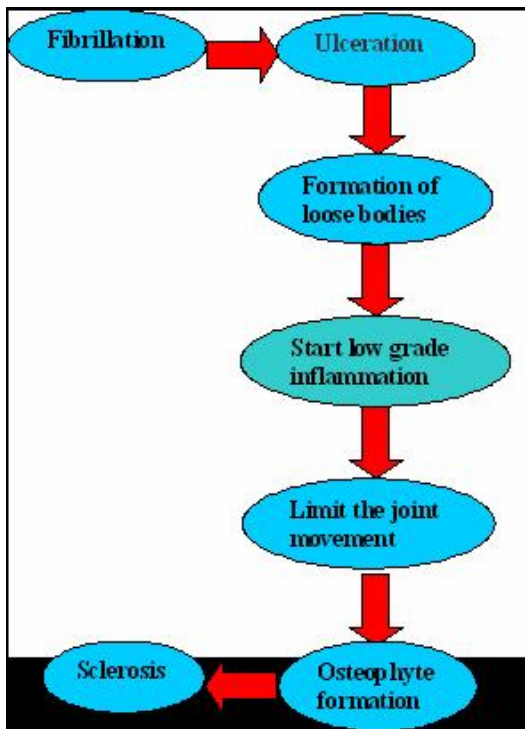


Figure 1: Pathophysiology of osteoarthritis

OBESITY

Overweight people are at considerably increased risk for the development of OA in their knees. They may also be more susceptible to both hip and hand joints involvement irrespective of the mechanisms. Weight reduction in a person through dietary or other means may reduce a risk for the development or progression of the OA⁹. Obese osteoarthritis patients were benefited from the weight loss and foods that supply the nutrients such as vitamin D, folacin, vitamin B6, zinc, and pantothenic acid in which they are deficient¹⁰. An intensive weight loss intervention incorporating deficit diet and exercise training improves physical function in older obese OA knee adults, greater improvements in function being directly proportional to the greater weight loss¹¹. **Miller et al**¹² performed longitudinal, controlled clinical trial of weight loss and exercise interventions in older adults with knee osteoarthritis to determine the effect of weight loss and exercise interventions on serum leptin and to investigate the relationship of physical function and osteoarthritis (OA) severity with serum leptin in older overweight and obese adults with knee OA. There was a significant

effect of weight loss on serum leptin. Decrease in serum leptin may be one mechanism by which weight loss improves physical function and symptoms in OA patients¹².

Recent research results indicate that an intensive weight-loss intervention in older obese adults with knee pain can help in improving inflammatory biomarkers- interleukin 6 (IL-6), tumor necrosis factor alpha (TNF α), C-reactive protein, and soluble receptors for TNF α (sTNFR1 and sTNFR2)) and that changes in these concentrations showed associations with physical function¹³.

REACTIVE OXYGEN SPECIES (ROS)

ROS is implicated in the pathophysiology of a number of common age related conditions¹⁴. OA similarly can be regarded as a prototypical age related degenerative disease. There is evidence that cells within the joint produces ROS, and that oxidative damage is physiologically important¹⁵. **Surapaneni et al**¹⁶ assessed oxidative stress and antioxidant status in patients with osteoarthritis. Levels of erythrocyte lipid peroxidation products, GSH, ascorbic acid, plasma vitamin E; and activities of antioxidant enzymes were measured in patients with osteoarthritis. The study suggests higher oxygen-free radical production evidenced by increased MDA and decreased GSH, ascorbic acid, vitamin E and catalase activity, support to the oxidative stress in osteoarthritis. The increased activities of antioxidant enzymes may be a compensatory regulation in response to increased oxidative stress¹⁶. Micronutrients might mediate the osteoarthritis process by blocking oxidative damage. Nitric oxide and reactive oxygen species inhibit collagen and proteoglycan synthesis, activate matrix metalloproteinases, increase the susceptibility of cartilage to injury by other oxidants, and induce apoptosis.

ASCORBIC ACID

Ascorbic acid (Asc) is required for the synthesis of the most abundant protein in cartilage, type II collagen. Asc exists in 2 forms: the reduced form (AA) and the oxidized form, dehydroascorbate (DHA). Both AA and DHA are available through the diet from fruits and vegetables and are absorbed throughout the entire length of the small intestine¹⁷. Diet constitutes the sole source of Asc for humans as they lack the enzyme gulonolactone oxidase which is necessary for the

synthesis of Asc from glucose¹⁸. Two distinct pathways of Asc transport across cellular membranes have been discovered to date, the sodium-dependent vitamin C transporters (SVCTs)¹⁹ and the glucose transporters (GLUTs)^{20,21}. The majority of vitamin C in plasma exists as AA, which is transported by the SVCTs²². It was recently shown that human chondrocytes express SVCT-2, but not SVCT-1. In contrast, the GLUTs are numerous and are ubiquitous in their expression. Of the GLUTs currently known to transport DHA, only GLUT-1 and GLUT-3 are expressed by human articular chondrocytes^{23,24}. However, the fact that has not taken into consideration is that articular cartilage is avascular and functions at a lower oxygen tension than most tissues. This may alter the tissue redox state and, thus, the local concentration of DHA, and/or it may regulate the transport pathways for DHA²⁵⁻²⁷. In vitro, ascorbate and ascorbic acid increased protein and proteoglycan synthesis by articular chondrocytes²⁸⁻³⁰ and increased the mRNA levels of type I and II collagen^{29,31} and aggrecan and α -prolyl 4-hydroxylase²⁷. It decreased the lipopolysaccharide (LPS)-induced GAG release³². It also affected the activities of lysosomal enzymes, decreasing the activities of arylsulfatase A and arylsulfatase B, an *N*-acetylgalactosaminidase-4-sulfatase, but increasing the activity of acid phosphatase in normal and OA chondrocytes³³. Ascorbic acid can cross-link collagen and other proteins by non-enzymatic glycation, leading to the formation of advanced glycation endproducts (AGEs). Threose, a metabolite of ascorbic acid, increases the AGE content of articular cartilage in vitro³⁴. These cross-links increase the stiffness of the collagen network, which is hypothesized to increase cartilage susceptibility to OA. High in vitro levels of ascorbic acid (756 μ M) also increased protein carbonylation, one type of oxidative damage. However, when guinea pigs were fed with diets containing different levels of ascorbic acid, no changes in the AGE content of articular cartilage were detected³⁵.

Schwartz and Adamy reported 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 the cartilage in the presence of ascorbic acid²⁹. **Manson et al**³⁴ suggested ascorbic acid stimulates collagen synthesis and modestly stimulates synthesis of aggrecan (a proteoglycan present in articular cartilage). Framingham

epidemiological study found a threefold reduction in risk of OA progression for both the middle and highest tertiles of vit C intake and an inverse association between vit C intake and cartilage loss³⁵. Guinea pigs do not possess gulonolactone enzyme which make them unable to synthesize ascorbic acid. Schwartz and Leveille in two studies showed that high vitamin C (which would correspond to vitamin C in humans of at least 500 mg/ day) is helpful in preventing cartilage fibrillation, structural changes in the joint and eburnation in guinea pigs³⁶. **Meacock** and colleagues on third guinea pig trial reported, an increase of extra ascorbic acid appeared to have some chondroprotective effect on the development of spontaneous lesions but gave no significant protection against surgically induced OA³⁷. The long term safety of such high doses of vitamin C in OA patients need to be evaluated and confirmed by long RCTs.

VITAMIN E

Natural vitamin E (vit E) comprises eight different forms, α -, β -, γ -, and δ -tocopherol and α -, β -, γ -, and δ -tocotrienol, produced solely by plants. **Tiku et al**³⁸ showed that when chondrocytes were submitted to an oxidative burst, vit E reduced the catabolism of collagen by preventing the protein oxidation mediated by aldehydic down products of lipid peroxidation. Vit E strongly increased glucosaminoglycan sulfatation or increased glucosaminoglycan synthesis while reducing glycoproteins or glycolipids synthesis. Like vit C, vit E affected the activities of lysosomal enzymes: it decreased the activities of arylsulfatase A and of acid phosphatase in cultures of human articular chondrocytes^{38,39}. There is some evidence suggesting that isoform concentrations relative to each other may be important in preventing specific types of oxidative damage⁴⁰⁻⁴³ with γ -tocopherol possibly being more important than α -tocopherol in removing nitrogen oxides and other electrophilic mutagens. Epidemiological studies examining the role of antioxidants, specifically tocopherols, in human osteoarthritis are few. Several methodologically limited clinical trials have suggested that vitamin E supplementation might be superior to placebo and equal in effectiveness to anti inflammatory medication in relieving osteoarthritis symptoms, but other studies have failed to show an effect⁴³⁻⁴⁷. To date, no studies have examined biomarkers of individual tocopherols in relation to radiographic knee osteoarthritis.

Black et al⁴⁸ demonstrated that incubation of rabbit articular cartilage with α -tocopherol preserved cartilage load-carrying capacity and viability. **Machtey et al**⁴³ in a six week double blind placebo controlled trial of 400 mg - a tocoferol (vitamin E) in 56 OA patients showed vitamin E treated patient's experienced greater improvement in every efficacy. **Mc Alindon et al**³⁵ showed vitamin E were associated with a reduced risk of progression of radiographic knee osteoarthritis but were not protective against incident disease. A randomized, double blind, placebo- controlled trial of 500 IU vitamin E daily to 77 patients for six months revealed neither vitamin E nor placebo showed a significant improvement in pain, stiffness, or physical function⁴⁵. One trial suggested that vit E was no less efficient than diclofenac in decreasing pain. In a 3-week double-blind RCT on OA, no significant difference was found between 544 mg of α -tocopherylacetate three times a day and 50 mg diclofenac three times a day on VAS of pain⁴⁹. On the other hand, a two-year randomized, double-blind, placebo-controlled trial examining the effect of vitamin E supplementation (500IU) on knee cartilage volume in 136 patients with OA of the knee showed no significant effect of supplemental vitamin E or the major dietary antioxidants (vitamin C, beta-carotene, or retinol activity equivalents) on the rate of loss of tibial knee cartilage⁴⁴. More recently, **Kurz et al**⁵⁰ reported that a diet containing vitamins E, C, A, B₆, and B₂ and selenium increased the expression of antioxidative enzymes and decreased the incidence of osteoarthritis in STR/1N mice. In the light of these results the role of vitamin E remains controversial and needs further longitudinal RCTs.

VITAMIN D

Vitamin D₃, or cholecalciferol, is synthesized in the skin. Its precursor, 7-dehydrocholesterol, is converted by the UV light of the sun (UVB 290–315 nm) into previtamin D₃, which is slowly isomerized to vitamin D₃. The action of 1,25-(OH)₂D on bone is not well understood. It stimulates the osteoblasts to produce osteocalcin and alkaline phosphatase and decreases the production of type I collagen by fetal rat calvaria⁵¹. On the other hand, 1,25-(OH)₂D stimulates bone resorption *in vitro*^{52,53}. The effects of 1,25-(OH)₂D on bone mineralization appear to be indirect by stimulating the calcium and phosphate supply, mainly by absorption from the gut.

Two longitudinal studies showed that vitamin D status is unrelated to the risk of joint space or cartilage loss in OA patients⁵⁴. A prospective study showed that low intake and low serum levels of vitamin D appears to be associated with an increased risk for the progression of OA Knee³⁵. **Lane NE**, in an eight years prospective study of 237 individuals (aged 65 years or older) showed that low serum levels of 25- hydroxyl vitamin D were associated with an increased risk of developing OA of the hip, as defined by joint-space narrowing⁵⁵. These findings suggests that adequate intake of vitamin D (adequate light exposure) may slow the progression of disease.

VITAMIN B

Researchers at the University of Southern California, School of Medicine in Los Angeles discovered that B₁₂ also stimulates osteoblasts, another type of bone cell that generates not red blood cells but bone. That is important to people with osteoarthritis, because below degenerating cartilage, bone also deteriorates, causing additional pain and further cartilage erosion. Researchers at the University of Missouri in Columbia found that people who took 20 micrograms of B₁₂ (3.3 times the daily value of 6 micrograms) and 6,400 micrograms of folic acid, for two months had fewer tender joints and better hand strength and took less medicine for pain than people not getting this B vitamin combo. The vitamin is thought to somehow improve the metabolism of joint cartilage.

Rosenberg et al⁵⁶ in a dietary survey of patients with OA found this population to have folate intakes lower than RDA. **William Kaufman** reported that high dose niacinamide a form of vitamin B₃ of 900-4000mg/day was beneficial in OA and as well as rheumatoid arthritis. He documented improvements in joint function, range of motion, increased muscle strength and endurance and reduction in erythrocyte sedimentation rate (ESR) over long findings in these patients⁵⁷. **Flynn et al**⁵⁸ diagnosed 26 subjects for an average 57 years with idiopathic OA of the joints in the hand and the number of tender hand joint was greater in those using NSAIDs when compared to cobalamin folate supplementation.

VITAMIN A (B- CAROTENE)

Machlin et al⁵⁹ and **Anderson et al**⁶⁰ indicated that antioxidants ascorbic acid, α -tocopherol and β -carotene are free radical scavenging nutrients that protect the cells from damage by pro-oxidants. **Martin et al**⁶¹ in a cross sectional study

showed lutein and zeaxanthin intake was associated with a decreased risk of cartilage defects and the β -cryptoxanthin intake was inversely associated with the tibial plateau bone area after adjusting for vitamin E intake. Other carotenoids were not significantly associated with cartilage or bone measures. Except for beta-carotene, none of the compounds examined in this study had been previously evaluated for involvement in the OA disease process. Participants with serum levels of lutein or beta-cryptoxanthin in the highest tertile were approximately 70% less likely to have knee OA than controls. Those in the highest tertile of trans- beta- carotene and zeaxanthin were more likely to have OA⁶².

VITAMIN K

Prospective observational cohort of Framingham Offspring Study on plasma phylloquinone (the primary form of vitamin K) showed that prevalence for osteophytes and the adjusted mean number of knee joints with osteophytes decreased significantly with increasing plasma phylloquinone level so it shows significantly an association between low plasma levels of vitamin K and increased prevalence of OA manifestations in the hand and knee⁶³.

MINERALS

In a case control study of synovial fluid and plasma concentrations of selenium (Se), zinc (Zn), copper (Cu) and iron (Fe) in patients with RA and OA, plasma albumin levels were measured as an index of nutritional status. Plasma Se, Cu and Zn concentrations were determined by atomic absorption spectrophotometry. There was a significantly positive correlation between synovial fluid Se and Cu values in patients with RA but not with OA⁶⁴. Walker et al⁶⁵ gave opinion that Zn plays a beneficial role in progression of OA due to anti-inflammatory and antioxidant property. A histological study of bone and articular cartilage was conducted on specimens from rats fed on low selenium (Se) diet. Electron microscopy disclosed chondrocytes in the deep layer showing degeneration of nuclei and endoplasmic reticular ballooning. A decrease in bone mineral density was noted, as well as a decrease in sulfotransferase activity, which is involved in synthesis of glycosaminoglycan⁶⁶. Femoral OA bone contains less boron, a nonmetallic trivalent chemical element which suggests that the boron might have a beneficial effect in OA⁶⁷. A small 8-week double-blind

placebo-controlled RCT suggested that intake of 6mg/day sodium tetraborate decahydrate was more efficient than placebo in reducing a patient's assessment scale of symptoms⁶⁸. This RCT, however, was of low quality hence, longer and higher-quality RCTs were required to evaluate thoroughly the benefits of boron for OA.

A small pilot study evaluated the impact of treatment with a natural multi-mineral supplement from seaweed on walking distance, pain and joint mobility in subjects with moderate to severe osteoarthritis of the knee. This small preliminary study suggested that a multi mineral supplement may reduce the pain and stiffness of osteoarthritis of the knee over 12 weeks of treatment and warrants further study⁶⁹.

POLYUNSATURATED FATTY ACIDS

Polyunsaturated fatty acids (PUFA) fall into 3 major classes the n-3, n-6, and n-9 groups. Specific long-chain polyunsaturated fatty acids (PUFA) belonging to omega-3 and omega-6 families are substrates for prostanoids that influence the differentiation and activity of cells in bone and cartilage tissues. These PUFA appear to alter prostanoid formation, cell-to-cell signaling processes, and impact transcription factors in vivo. Watkins et al⁷⁰ reported that dietary fatty acids and their derivatives (eicosanoids) represent a recent focus of investigation on bone and cartilage metabolism. Epidemiological, clinical and experimental evidence suggests that fatty acids may have an effect (due to their chemical structure) on calcium metabolism in animals and man. Fatty acid deficiency in animals can lead to a loss of bone calcium and matrix, resulting in, marked bone demineralization, and treatment with a mixture of omega-3 and omega-6 polyunsaturated fatty acids can induce significant reduction in some biochemical markers of bone reabsorption⁷¹. Colker et al⁷² in their six week double blind placebo control study showed that daily consumption of the nutritional beverage containing milk based micro nutrients vitamins and minerals was beneficial in alleviating the symptoms and dysfunction in subjects with osteoarthritis. Pritchett⁷³ showed that taking fish oils reduced the amount of lipid in bone marrow by 20%. Lipid profiles of disturbed marrow and joint fluid from patients who took statins or dietary fish oil showed an increase in the proportion of unsaturated fatty acids and longer-chain fatty acids relative to pretreatment profiles. The ability to change the

amount and character of bone and joint lipids may have major importance for strengthening bone, reducing the severity or preventing osteonecrosis, and enhancing joint lubrication⁷⁵. **Sperling**⁷⁴ said the increase consumption of n-3 fatty acid ameliorates the symptoms of OA. In vitro, effects of 10 to 100µg/ml of n-3 (linolenic, eicosapentaenoic, and docosahexaenoic acids) on chondrocytes have been investigated. n-3 did not affect the spontaneous or the IL1-induced decrease in glycosaminoglycan (GAG) synthesis, but dose-dependently inhibited the IL1-induced GAG degradation. n-3 dose-dependently decreased the IL1-induced aggrecanase activity and basal aggrecanase and collagenase activity, whereas, in contrast, n-6 stimulated the basal aggrecanase and collagenase activity⁷⁴⁻⁷⁷. n-3 also decreased the IL1-induced mRNA expression of ADAMTS-4 (aggrecanase), COX-2, 5-LOX, FLAP (5-LOX-activating protein), IL1 α , and tumour necrosis factor (TNF) α and the basal mRNA levels of these genes. Finally, n-3 decreased the basal and IL1 β -induced mRNA and protein levels of MMP-3 and MMP-13. All these parameters were unaffected by n-6 PUFAs. Taken together, these results indicate that n-3 PUFAs have anticatabolic and anti-inflammatory properties. Nevertheless, too low of an n-6/n-3 ratio can be detrimental. A diet with very low levels of n-6 PUFAs induced occasional surface irregularities and localised proteoglycan depletion in cartilages in rats⁷⁸.

Watkins et al⁷⁹ in recent investigations with growing rats given butter fat and supplements of CLA demonstrated an increased rate of bone formation and reduced ex vivo bone PGE2 production, respectively. The effects of CLA on bone biology in rats (IGF action and cytokines) appear to be dependent on the level of n6 and n-3 fatty acids in the diet, Anti-inflammatory diets, including nutraceutical applications of CLA, may be beneficial in moderating cyclooxygenase -2 (COX-2) activity or expression (influencing PGE2 biosynthesis) and might help to reduce rheumatoid arthritis (secondary osteoporosis). This experiment indicates that CLA isomers possess anti-inflammatory activity in bone by moderating prostanoid formation.

PHYTOCHEMICALS AND PLANT EXTRACTS

Flavonoids, a group of polyphenolic compounds widely distributed throughout the plant kingdom, are thought to contribute to the health benefits of diets rich in fruits and vegetables. In vivo effects of several flavonoids (tea-containing catechins,

soy isoflavones) have been reported in the literature. **Perdey et al**⁸⁰ reported that plants derived phenolic compounds such as flavonoids have antioxidant properties capable of reducing risk of developing these joint diseases. **Bromelain** (aqueous extract obtained from both the stems and immature fruits of pineapple plant) contain a number of proteolytic enzymes. Bromelain is suggested to have anti-inflammatory, analgesic, antioedematous, antithrombotic, and fibrinolytic effects. Three different preparations containing bromelain mixed with diverse enzymes have been tested in nine trials on knee OA^{81,82}. **Rosa canina** a standardised rose-hip powder made from the seeds and husks of the fruits from a subtype of *R. canina* (Hyben Vital™ produced by Hyben Vital International, Langeland, Denmark), and the common wild-briar rose of English hedgerows, were evaluated in three RCTs^{83,84}. **Harpagophytum procumbens** also called devil's claw, is a South African plant that grows in regions bordering the Kalahari, is used for exacerbations of chronic musculoskeletal pain. Secondary tuberous roots are used to prepare powders or extracts, which were tested in several RCTs⁸⁵. **Uncaria tomentosa and Uncaria guianensis (cat's claw)** is a vine from the basin of the Amazon River. There are two species, *U. tomentosa* and *U. guianensis*, which are traditionally used in South America for their anti-inflammatory properties⁸⁶. The anti-inflammatory, antipyretic, and analgesic effects of **Salix sp. (willow bark)** have been known since antiquity⁸⁷.

GINGER AND TURMERIC

Ginger and turmeric are used in traditional Japanese Kampo, Ayurvedic, and Chinese medicine as anti-inflammatory agents for musculoskeletal diseases. Three RCTs evaluated ginger extracts prepared from the rhizomes of **Zingiber officinale** and **Alpinia galanga**. An extract prepared from the Indian and Japanese turmeric **Curcuma domestica** and **Curcuma xanthorrhiza**, was tested on hip and elbow OA in an 8-week double-blind randomised trial in dogs⁸⁸. No significant difference on the kinetic gait analysis was found between extract and placebo. The gummy oleoresin from the bark of **Boswellia serrata**, a tree from northwest India, is used for inflammatory diseases in Ayurvedic medicine⁸⁹. The pilot clinical trial conducted by Douglas S showed that daily supplementation with oral hyaluronic acid from a natural extract of chicken combs was useful to enhance several

markers of quality of life in adults with osteoarthritis of the knee. The results warrant further study in larger sample sizes⁹⁰.

DISCUSSION AND CONCLUSION

The nutritional factors tested in above mentioned studies such as vitamins C, D, E, A, B, minerals (Zinc, Selenium, Boron), lipids (polyunsaturated fatty acids), and Plant extracts like flavonoid, bromelain, *Rosa canina*, *Harpagophytum procumbens* (devil's claw), *Uncaria tomentosa*, *Uncaria guianensis* (cat's claw), *Salix sp.* (willow bark) suggest correlation in the progression of OA. Evidences suggest weight reduction in a person through dietary or other means reduces the risk for development and/or progression of the OA. Vitamin C has been found to have chondroprotective effect especially in high doses. Low intake and low serum levels of vitamin D appear to be associated with an increase risk for the progression of OA knee. Role of vitamin E remains controversial and needs further longitudinal studies. The evidence of efficacy and the safety records of plant extracts should be considered to be product specific given that the composition of the extracts from a same plant can vary widely between manufacturers. The vitamins and some of the lipids reviewed here are sold as nutraceuticals but can also be incorporated in functional foods.

Nutrition can improve the symptoms of declared OA. However, the role of nutrition in slowing down progression of disease remains to be seen. Only a few nutrients have been tested, and research remains mainly on a pharmacological type of approach (one molecule/one target) rather than on a nutritional, more holistic type of approach (multiple ingredients/ multiple targets). The full potency of nutrition for patients with declared OA thus remains to be evaluated. No study has evaluated the value of nutrition in the prevention of OA. Based on the above review, we can conclude that nutritional factors have proven role in improvement of the disease condition in OA. While planning the prescription for any patient, we should not forget that Vitamin C, D, Boron, plant extracts such as flavanoids, bromelain, etc should be adequately supplemented or enriched in the diet so that the pathology of the disease is well taken care of. These factors have established role in the management of OA. Besides them, other factors have also shown beneficial effect in the cartilage-regeneration. Their supplementation can decrease the rate of disease progression.

LIST OF ABBREVIATION

CLA: Conjugated Linoleic Acid; PUFA: Poly Unsaturated Fatty Acid; GSH: Gastro Stimulating Hormones; OA: Osteoarthritis; GAG: Glycosaminoglycan; PGE: Prostaglandin E; AGE's: Advanced Glycation Endproducts; COX-2: Cyclooxygenase-2; DHA: Dehydroascorbate

REFERENCES

1. Nuki G. Osteoarthritis: a problem of joint failure. *Z Rheumatol.* 1999 June;58(3):142-7.
2. Yelin E. The economics of osteoarthritis. In *Osteoarthritis.* Oxford University Press; Oxford:2003:17-21.
3. Kellgren JH, Lawrence JS, Bier F. Genetic factors in generalized osteo-arthrosis. *Ann Rheum Dis.* 1963 Jul;22:237-55.
4. Felson DT, Hannan MT, Naimark A, et al. Occupational physical demands, knee bending, and knee osteoarthritis results from the Framingham study. *J Rheumatol.* 1991 Oct;18(10):1587-92.
5. Chaisson C, Zhang Y, McAlindon TE, et al. Radiographic hand osteoarthritis: incidence, patterns, and influence of pre-existing disease in a population based sample. *J Rheumatol.* 1997 Jul;24(7):1337-43.
6. Felson DT, Zhang Y, Hannan MT, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham study. *Arthritis rheum.* 1997 Apr;40(4):728-33.
7. Brandt KD. Effects of nonsteroidal anti-inflammatory drugs on chondrocyte metabolism in vitro and vivo. *Am J Med.* 1987 Nov; 83(5A):29-34.
8. Rashad S, Revell P, Hemingway A, et al. Effect of non-steroidal anti-inflammatory drugs on the course of osteoarthritis. *Lancet* 1989 Sep;2(8662):519-22.
9. Felson DT, Zhang Y, Anthony JM, et al. Weight loss reduces the risk for symptomatic knee osteoarthritis in women. The Framingham Study. *Ann Intern Med.* 1992 Apr; 116(7):533-9.
10. White-O'Connor B, Sobal J. Nutrient intake and obesity in a multidisciplinary assessment of osteoarthritis. *Clin Ther.* 1986;9 suppl B: 30-42.
11. Wang X, Miller GD, Messier SP, et al. Knee strength maintained despite loss of lean body mass during weight loss in older obese adults with knee osteoarthritis. *J Gerontol A Biol Sci Med Sci.* 2007 Aug;62(8):866-71.

12. Miller GD, Nicklas BJ, Davis CC, et al. Is serum leptin related to physical function and is it modifiable through weight loss and exercise in older adults with osteoarthritis? *Int J Obes Relat Metab Disord.* 2004 Nov;28(11):1383-90.
13. Miller GD, Nicklas BJ, Loeser RF. Inflammatory biomarkers and physical function in older, obese adults with knee pain and self-reported osteoarthritis after intensive weight-loss therapy. *J Am Geriatr Soc.* 2008 Apr;56(4):644-51.
14. Jacques PF, Chylack LI, Taylor A. Relationship between natural antioxidants and cataract formation. In Frei B (ed) *Natural antioxidants in human health and disease.* San Diego, CA: Academic press, 1994:515-33.
15. Briviba K, Sies H. Non enzymic antioxidant defense system. In Frei B. (ed) *Natural antioxidants in human health and disease.* San Diego, CA: Academic press, 1994:107-28.
16. Surapaneni KM, Venkataramana G. Status of lipid peroxidation, glutathione, ascorbic acid, vitamin E and antioxidant enzymes in patients with osteoarthritis. *Indian J Med Sci.* 2007 Jan;61(1):9-14.
17. Malo C, Wilson JX. Glucose modulates vitamin C transport in adult human small intestinal brush border membrane vesicles. *J Nutr.* 2000 Jan;130(1):63-9.
18. Burns JJ. Missing step in man, monkey and guinea pig required for the biosynthesis of L-ascorbic acid. *Nature.* 1957 Sep;180(4585):553.
19. Tsukaguchi H, Tokui T, Mackenzie B, et al. A family of mammalian Na⁺-dependent L-ascorbic acid transporters. *Nature.* 1999 May;399(6731):70-5.
20. Vera JC, Rivas CI, Fischbarg J, et al. Mammalian facilitative hexose transporters mediate the transport of dehydroascorbic acid. *Nature.* 1993 Jul;364(6432):79-82.
21. Rumsey SC, Kwon O, Xu GW, et al. Glucose transporter isoforms GLUT1 and GLUT3 transport dehydroascorbic acid. *J Biol Chem.* 1997 Jul;272(30):18982-9.
22. McNulty AL, Vail TP, Kraus VB. Chondrocyte transport and concentration of ascorbic acid is mediated by SVCT2. *Biochim Biophys Acta.* 2005 Jun;1712(2):212-21.
23. Shikhman AR, Brinson DC, Valbracht J, et al. Cytokine regulation of facilitated glucose transport in human articular chondrocytes. *J Immunol.* 2001 Dec;167(12):7001-8.
24. Mobasheri A, Neama G, Bell S, et al. Human articular chondrocytes express three facilitative glucose transporter isoforms: GLUT1, GLUT3 and GLUT9. *Cell Biol Int.* 2002;26(3):297-300.
25. Richardson S, Neama G, Phillips T, et al. Molecular characterization and partial cDNA cloning of facilitative glucose transporters expressed in human articular chondrocytes; stimulation of 2-deoxyglucose uptake by IGF-1 and elevated MMP-2 secretion by glucose deprivation. *Osteoarthritis Cartilage.* 2003 Feb;11(2):92-101.
26. Silver IA. Measurement of pH and ionic composition of pericellular sites. *Philos Trans R Soc Lond B Biol Sci.* 1975 Jul;271(912):261-72.
27. Zhou S, Cui Z, Urban JP. Factors influencing the oxygen concentration gradient from the synovial surface of articular cartilage to the cartilage-bone interface: a modeling study. *Arthritis Rheum.* 2004 Dec;50(12):3915-24.
28. Clark AG, Rohrbaugh AL, Otterness I, et al. The effects of ascorbic acid on cartilage metabolism in guinea pig articular cartilage explants. *Matrix-Biol.* 2002 Mar;21(2):175-84.
29. Schwartz ER, Adamy L. Effect of ascorbic acid on arylsulfatase activities and sulfated proteoglycan metabolism in chondrocyte cultures. *J Clin Invest.* 1977 Jul;60(1):96-106.
30. Daniel JC, Pauli BU, Kuettner KE. Synthesis of cartilage matrix by mammalian chondrocytes in vitro. III. Effects of ascorbate. *J Cell Biol.* 1984 Dec;99(6):1960-9.
31. Sandell LJ, Daniel JC. Effects of ascorbic acid on collagen mRNA levels in short term chondrocyte cultures. *Connect Tissue Res.* 1988;17(1):11-22.
32. Tiku ML, Gupta S, Deshmukh DR. Aggrecan degradation in chondrocytes is mediated by reactive oxygen species and protected by antioxidants. *Free Radic Res.* 1999 May;30(5):395-405.
33. Verzijl N, DeGroot J, Ben ZC, et al. Crosslinking by advanced glycation end products increases the stiffness of the collagen network in human articular cartilage: a possible mechanism through

- which age is a risk factor for osteoarthritis. *Arthritis Rheum.* 2002 Jan;46(1):14-23.
34. Manson JF, Stampfer MJ, Willett WC. A prospective study of antioxidants vitamins and incidence of coronary artery disease in women. *Circulation.* 1991;84 (suppl):2168.
 35. McAlindon TE, Jacques P, Zhang Y, et al. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? *Arthritis Rheum* 1996 Apr;39(4):648-56.
 36. Schwartz ER, Leveille C, Oh WH. Experimentally-induced osteoarthritis in guinea pigs: effect of surgical procedure and dietary intake of vitamin C. *Lab Anim Sci.* 1981 Dec;31(6):683-7.
 37. Meacock SC, Bodmer JL, Billingham ME. Experimental osteoarthritis in guinea pigs. *J Exp Pathol (Oxford).* 1990 Apr;71(2): 279-93.
 38. Tiku ML, Shah R, Allison GT. Evidence linking chondrocyte lipid peroxidation to cartilage matrix protein degradation. Possible role in cartilage aging and the pathogenesis of osteoarthritis. *J Biol Chem.* 2000 Jun;275(26):20069-76.
 39. Schwartz ER. Effect of vitamins C and E on sulfated proteoglycan metabolism and sulfatase and phosphatase activities in organ cultures of human cartilage. *Calcif Tissue Int.* 1979 Nov;28(3):201-8.
 40. Jiang Q, Elson-Schwab I, Courtemanche C, et al. Gamma-tocopherol and its major metabolite, in contrast to alpha-tocopherol, inhibit cyclooxygenase activity in macrophages and epithelial cells. *Proc Natl Acad Sci U S A.* 2000 Oct;97(21):11494-9.
 41. Ingles SA, Bird CL, Shikany JM, et al. Plasma tocopherol and prevalence of colorectal adenomas in a multiethnic population. *Cancer Res.* 1998 Feb;58(4):661-6.
 42. Ohrvall M, Sundlof G, Vessby B. Gamma but not alpha, tocopherol levels in serum are reduced in coronary heart disease patients. *J Intern Med.* 1996;239:111-7.
 43. Machtay I, Ouaknine L. Tocopherol in osteoarthritis: a controlled pilot study. *J Am Geriatr Soc.* 1978 Jul;26(7):328-30.
 44. Wluka AE, Stuckey S, Brand C, et al. Supplementary vitamin E does not affect the loss of cartilage volume in knee osteoarthritis: a 2 year double blind randomized placebo controlled study. *J Rheumatol.* 2002 Dec;29(12):2585-91.
 45. Brand C, Snaddon J, Bailey M, et al. Vitamin E is ineffective for symptomatic relief of knee osteoarthritis: a six month double blind, randomised, placebo controlled study. *Ann Rheum Dis.* 2001 Oct;60(10):946-9.
 46. Blankenhorn G. Clinical effectiveness of Spondyvit (vitamin E) in activated arthroses: a multicenter placebo-controlled double-blind study. *Z Orthop Ihre Grenzgeb.* 1986 May-June;124(3):340-3.
 47. Scherak O, Kolarz G, Schodl C, et al. High dosage vitamin E therapy in patients with activated arthrosis. *Z Rheumatol.* 1990 Nov-Dec;49(6):369-73.
 48. Black J, Shadle CA, Parsons JR, et al. Articular cartilage preservation and storage. II. Mechanical indentation testing of viable, stored articular cartilage. *Arthritis Rheum.* 1979 Oct;22(10):1102-8.
 49. Nierenberg DW, Stukel T. Diurnal variation in plasma levels of retinol, tocopherol, and beta-carotene. *Am J Med Sci.* 1987 Sep;294(3):187-90.
 50. Kurz B, Jost B, Schunke M. Dietary vitamins and selenium diminish the development of mechanically induced osteoarthritis and increase the expression of antioxidative enzymes in the knee joint of STR/1N mice. *Osteoarthritis Cartilage.* 2002 Feb;10(2):119-26.
 51. Holick MF. Vitamin D and the skin: photobiology, physiology and therapeutic efficacy for psoriasis. *Bone and Mineral Research.* Seventh Edition. Amsterdam: Elsevier 1999;313-66.
 52. DeLuca HF. The vitamin D story: a collaborative effort of basic science and clinical medicine. *FASEB J.* 1998 Mar;2(3):224-36.
 53. Walters MR. Newly identified actions of the vitamin D endocrine system. *Endocr Rev.* 1992 Nov;13(4):719-64.
 54. Felson DT, Niu J, Clancy M, et al. Low levels of vitamin D and worsening of knee osteoarthritis: results of two longitudinal studies. *Arthritis Rheum.* 2007 Jan;56(1):129-36.
 55. Lane NE, Gore LR, Cummings SR, et al. Serum vitamin D levels and incident changes of radiographic hip osteoarthritis: a longitudinal study. Study of Osteoporotic Fractures Research Group. *Arthritis Rheum.* 1999 May;42(5):854-60.

56. Rosenberg IH, Bowman BB, Cooper BA, et al. Folate nutrition in the elderly. *Am J Clin Nutr.* 1982 Nov;36(5 Suppl):1060-6.
57. Kaufman W. Niacinamide therapy for joint mobility; therapeutic reversal of a common clinical manifestation of the normal aging process. *Conn Med.* 1953 Jul;17(7):584-9.
58. Flynn MA, Irvin W, Krause G. The effect of folate and cobalamin on osteoarthritic hands. *J Am Coll Nutr.* 1994 Aug;13(4):351-6.
59. Machlin L, Bendich A. Free radical tissue damage: protective role of antioxidants nutrients. *FASEB J.* 1987 Dec;1(6):441-5.
60. Anderson R, Theron AJ. Physiological potential of ascorbate, beta-carotene and alpha-tocopherol individually and in combination in the prevention of tissue damage, carcinogenesis and immune dysfunction mediated by phagocyte-derived reactive oxidants. *World Rev Nutr Diet.* 1990;62:27-58.
61. Martin KR, Failla ML, Smith JC Jr. Beta carotene and lutein protect HepG2 human liver cells against oxidant-induced damage. *J nutr.* 1996 Sep;126(9):2098-106.
62. De Roos AJ, Arab L, Renner JB, et al. Serum carotenoids and radiographic knee osteoarthritis. the Johnston County Osteoarthritis Project. *Public Health Nutr.* 2001 Oct;4(5):935-42.
63. Neogi T, Booth SL, Zhang YQ, et al. Low Vitamin K status is associated with osteoarthritis in the hand and knee. *Arthritis Rheum.* 2006 April;1255-61.
64. Yazar M, Sarban S, Kocyigit A, et al. Synovial fluid and plasma selenium, copper, zinc, and iron concentrations in patients with rheumatoid arthritis and osteoarthritis. *Biol Trace Elem Res.* 2005 Aug;106(2):123-32.
65. Walker WR, Keats DM. An investigation of the therapeutic value of the 'copper bracelet': dermal assimilation of copper in arthritic/rheumatoid conditions. *Agents Actions.* 1976 Jul;6(4):454-9.
66. Tarp U, Overvad K, Thorling EB, et al. Selenium treatment in rheumatoid arthritis. *Scand J Rheumatol.* 1985;14(4):364-8.
67. Newnham RE. Essentiality of boron for healthy bones and joints. *Environ Health Perspect.* 1994 Nov;102 Suppl 7:83-5.
68. Frestedt JL, Walsh M, Kuskowski MA, et al. A natural mineral supplement provides relief from knee osteoarthritis symptoms: a randomized controlled pilot trial. *Nutr J.* 2008 Feb 17;7:9.
69. Darlington LG, Stone TW. Antioxidants and fatty acids in the amelioration of rheumatoid arthritis and related disorders. *Br J Nutr.* 2001 Mar;85(3):251-69.
70. Watkins BA, Li Y, Seifert MF. Nutraceutical fatty acids as biochemical and molecular modulators of skeletal biology. *J Am Coll Nutr.* 2001 Oct;20(5 Suppl):410S-416S.
71. Baggio B. Fatty acids, calcium and bone metabolism. *J Nephrol.* 2002 Nov-Dec;15(6):601-4.
72. Colker CM, Swain M, Lynch L, et al. Effects of a milk-based bioactive micronutrient beverage on pain symptoms and activity of adults with osteoarthritis: a double-blind, placebo-controlled clinical evaluation. *Nutrition.* 2002 May;18(5):388-92.
73. Pritchett JW. Statins and dietary fish oils improve lipid composition in bone marrow. *Clin Orthop Relat Res.* 2007 Mar;456:233-7.
74. Sperling RI. Dietary omega-3 fatty acids: effect on lipid mediators of inflammation and rheumatoid arthritis. *Rheum Dis Clin North Am.* 1991 May;17(2):735-89.
75. Curtis CL, Hughes CE, Flannery CR, et al. n-3 fatty acids specifically modulate catabolic factors involved in articular cartilage degradation. *J Biol Chem.* 2000 Jan;275(2):721-4.
76. Curtis CL, Rees SG, Cramp J, et al. Effects of n-3 fatty acids on cartilage metabolism. *Proc Nutr Soc.* 2002 Aug;61(3):381-9.
77. Curtis CL, Rees SG, Little CB, et al. Pathologic indicators of degradation and inflammation in human osteoarthritic cartilage are abrogated by exposure to n-3 fatty acids. *Arthritis Rheum.* 2002 Jan;46(6):1544-53.
78. Lippiello L, Fienhold M, Grandjean C. Metabolic and ultrastructural changes in articular cartilage of rats fed dietary supplements of omega-3 fatty acids. *Arthritis Rheum.* 1990 Jul;33(7):1029-36.
79. Watkins BA, Seifert MF. Conjugated linoleic acid and bone biology. *J Am Coll Nutr.* 2000 Aug;19(4):478S-486S.
80. Pendrey B, Busia K, Bell CM. Phytochemical evaluation of selected antioxidant containing medicinal plants for use in the preparation of a herbal formula--a preliminary study. *Chem Biodivers.* 2005 Jul;2(7):917-22.

81. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. *Cell Mol Life Sci.* 2001 Aug; 58(9):1234-45.
82. Brien S, Lewith G, Walker A, et al. Bromelain as a Treatment for Osteoarthritis: a Review of Clinical Studies. *Evid Based Complement Alternat Med.* 2004 Dec;1(3):251-7.
83. Warholm O, Skaar S, Hedman E, et al. The effects of a standardized herbal remedy made from a subtype of *Rosa canina* in patients with osteoarthritis: A double-blind, randomized, placebo-controlled clinical trial. *Curr Ther Res.* 2003;64(1):21-31.
84. Rein E, Kharazmi A, Winther K. A herbal remedy, Hyben Vital (stand. powder of a subspecies of *Rosa canina* fruits), reduces pain and improves general wellbeing in patients with osteoarthritis--a double-blind, placebo-controlled, randomised trial. *Phytomedicine.* 2004 Jul;11(5):383-91.
85. Chrubasik S, Conrath C, Black A. The quality of clinical trials with *Harpagophytum procumbens*. *Phytomedicine.* 2003;10(607):613-23.
86. Sandoval M, Okuhama NN, Zhang XJ, et al. Anti-inflammatory and antioxidant activities of cat's claw (*Uncaria tomentosa* and *Uncaria guianensis*) are independent of their alkaloid content. *Phytomedicine.* 2002 May;9(4):325-337.
87. Mills SY, Jacoby RK, Chacksfield M, et al. Effect of a proprietary herbal medicine on the relief of chronic arthritic pain: a double-blind study. *Br J Rheumatol.* 1996 Sep;35(9):874-8.
88. Innes JF, Fuller CJ, Grover ER, et al. Randomised, double-blind, placebo-controlled parallel group study of P54FP for the treatment of dogs with osteoarthritis. *Vet Rec.* 2003 Apr;152(15):457-60.
89. Kimmatkar N, Thawani V, Hingorani L, Khiyani R. Efficacy and tolerability of *Boswellia serrata* extract in treatment of osteoarthritis of knee--a randomized double blind placebo controlled trial. *Phytomedicine.* 2003 Jan;10(1):3-7.
90. Kalman DS, Heimer M, Valdeon A, et al. Effect of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal-Joint) on pain relief and quality of life in subjects with knee osteoarthritis: a pilot randomized double-blind placebo-controlled trial. *Nutr J.* 2008 Jan 21;7:3.