



Nutritional Perspectives



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Osteoarthritis and Nutritional Support: A Literature Review

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Abstract

Osteoarthritis (OA) appears to be one for the unfortunate consequences of the evolution of the bony skeleton. Despite much study in other areas, the impact of diet in terms of caloric balance and the biochemical effects of essential nutrients is only just being explored. There is little question that proper weight control will positively influence the course of osteoarthritis of some joints. When it comes to the role of non-caloric essential nutrients the impact is less clear. A number of studies have shown that a large percentage of patients with OA are ingesting less than the US RDA for vitamins A, C, D, E, pyridoxin, folacin, pantothenic acid and the minerals zinc, magnesium, iron and calcium. Many substances such as vitamins A, C, E, niacin and sulfur have shown promising results in initial studies with osteoarthritis. However much, much more work remains to be done and until these studies are performed any clinical recommendations in megadose ranges for vitamin and mineral supplementation by OA patients should remain guarded.

Introduction

Osteoarthritis (OA) appears to be one of the unfortunate consequences in the evolution of the bony skeleton. It is present in almost all mammals and was present in prehistoric mammals as well^(1,2). In man, the question of whether diet can influence the signs, symptoms and degenerative changes associated with osteoarthritis is particularly important for those health care practitioners who treat such patients. Chiropractors in particular, due to the nature of their practice, are continually challenged by the problems surrounding the degenerating joint. Although in many cases manipulative and adjunctive physical modalities can offer relief to these patients, the impact of diet in terms of caloric balance and the biochemical effects of essential nutrients is only just being explored.

It is now known that primary OA is not strictly associated with aging as a result of the normal "wear and tear" process. Indeed, there is evidence to suggest that there are multiple etiologies for osteoarthritis which is not secondary to metabolic or hormonal imbalance. Recent reports suggest that there is a hereditary predisposition for OA. Two genetic sites have been implicated, one which involves an alteration in the gene for Type II procollagen⁽³⁾, and a second which involves the manufacturing of the protease inhibitor alpha 1-antichymotrypsin⁽⁴⁾. On the other hand, non-genetically based OA appears to be induced through macro or micro trauma initiated shear stresses⁽⁵⁾. However, once this form has begun it is not inexorably progressive. According to Bland⁽⁶⁾: "there is a firm body of evidence in clinical and experimental OA research that the process can often be arrested and occasionally reversed."

As none of the previous clinical trials distinguished between the genetic or mechanical types of primary osteoarthritis, all results from these studies must now be viewed from a new perspective. Whether genetic forms of OA can be affected through dietary means must be addressed in light of this new information. In any event, it is beyond the scope of practice for most general practitioners to assess their patient's genetic blueprint. And those studies which have been performed to date invariably included members with a mix of the possible etiological factors, just as any general practice

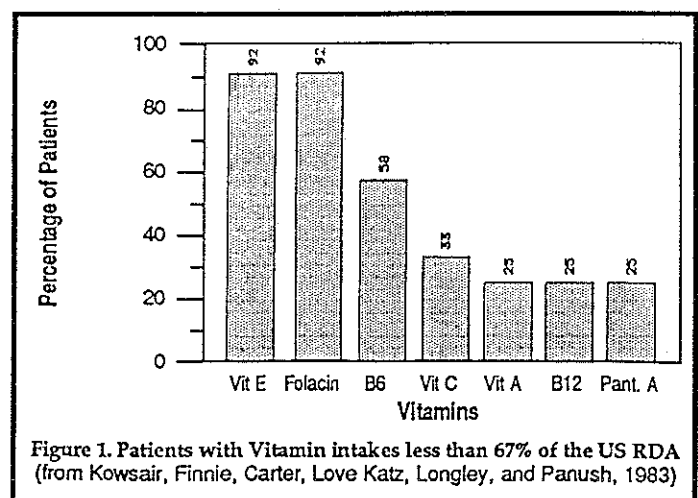
would and therefore it is still valuable to see what has been done to date.

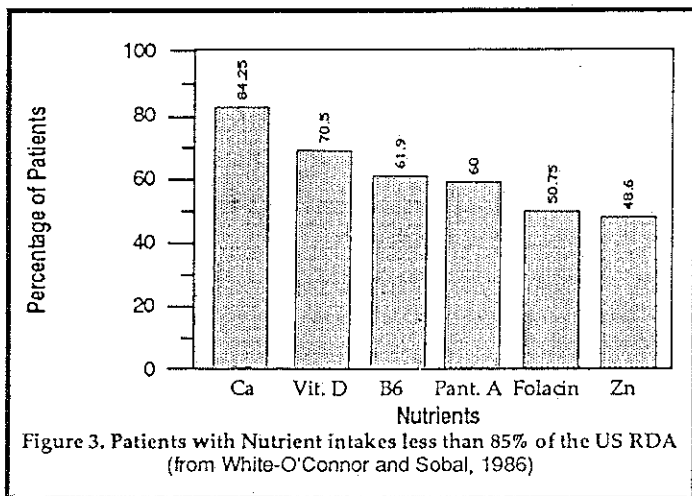
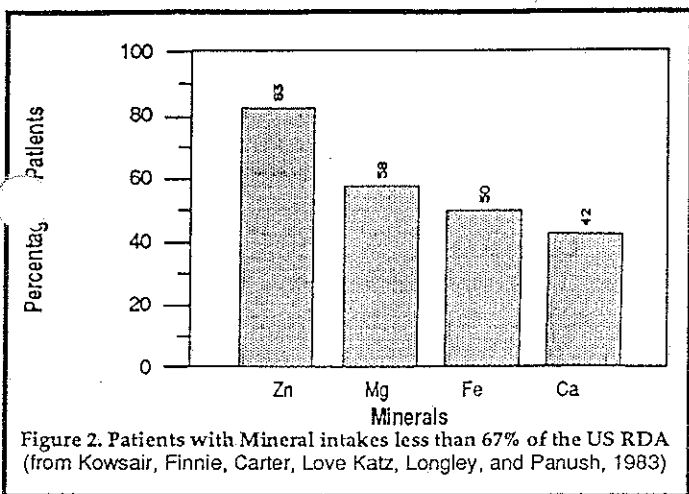
While most previous scientific studies have been used with a physical or pharmacological primary therapeutic approach, there is a growing body of evidence which supports the use of the nutritional approach as well. Caloric imbalance has already been shown to have a direct effect on joint degeneration. Obesity, for example, has been shown in a number of studies to be associated with osteoarthritis, particularly the painful lesion⁽⁷⁾. According to Mascioli and Blackburn⁽⁸⁾ the prevalence of OA in both weight bearing and non-weight bearing joints of obese individuals is nearly twice that of normal weight individuals. They feel it accelerates cartilage breakdown which may then lead to an aggravation of the patient's symptoms. Acheson and Collart⁽⁹⁾ found a greater prevalence of osteoarthritis among the obese when compared to their thin counterparts, while Julkunen, Kiehela and Julkeunen⁽¹⁰⁾ also discovered a slight increase (5%) in obesity in a group of osteoarthritis when compared to a control group.

Whether obesity causes osteoarthritis through increased compressive loading or whether osteoarthritis leads to obesity through incapacitation is not clearly understood. Regardless, when obesity and osteoarthritis occur together weight loss in the obese will certainly reduce the strain on the weight-bearing structures, thus relieving pain and increasing activity. The impact of other dietary factors however, is not so clear cut.

Non-caloric Essential Nutrient Intake

To determine whether OA patients should make dietary changes besides monitoring caloric intake, it is first important to assess their baseline nutritional status. An early study by Eisin⁽¹¹⁾ was not completely comprehensive in its analysis of essential nutrient intakes. Indeed only calcium, iron, phosphorus, magnesium, vitamins A, C, thiamin, riboflavin, niacin and pyridoxine were assessed. Even so, calcium, magnesium, thiamin and pyridoxine were found to be deficient. A later report by Kowasari, Finnie, Carter, Love, Katz, Longley, and Panush⁽¹²⁾ showed that a large percentage of patients with symptomatic osteoarthritis were ingesting less than 67% of the United States RDA's for vitamins E, C, A, B₁₂, pyridoxine, folacin, and pantothenic acid (Fig. 1). Those minerals which were not being ingested in adequate amounts included zinc, magnesium, iron and calcium (trace minerals were not assessed) (Fig. 2). Although their patient sample was small (n=12) it did include members of all socioeconomic groups. In a larger group study, White-O'Connor and Sobal⁽⁷⁾ collected dietary information about 77 OA patients over a 12 week period. They found mean dietary intakes of





ins B₆, D, folacin, and pantothenic acid and the minerals zinc and calcium to be below 85% of the US RDA level for persons aged 51 or older (Fig. 3). While their study only reported average intakes for the group and did not report the number of individuals within the group who were deficient, it still supports the notion that there is a problem in achieving adequate nutrient intake for some osteoarthritics when comparing their intakes to the US RDA.

Whether these deficiencies were causative or a result of the patient's disability cannot be determined by these types of surveys. There was, however, a clear indication that nutritionally counseling might be an important aspect of their clinical care. The question becomes more complicated though when trying to determine which nutrients and at what levels a specific patient should possibly supplement. If supplementation is being considered, there are primarily three avenues of thought depending on the clinical rationale used:

1. Treat the patient as an otherwise health individual and only supplement to achieve ingestion of essential nutrients to levels approximating the RDA.
2. Accept the hypothesis that these patients have special nutritional needs and require greater intakes of essential nutrients beyond the RDA levels just to achieve adequate levels within the body.
3. Accept the hypothesis that some essential and non-essential nutrients have pharmacological/chemical properties which positively affect the course of the disease and may be needed in amounts far greater than the RDA to have that effect.

As in most clinical situations the best answer is probably an amalgamation of the possible therapies, with the patient being the most important factor in determining the mix. However, in order to try to determine what is best for an individual patient, initially it is

probably prudent to attempt to identify which substances he is deficient in.

One of the best methods of assessing nutrient intake is through the quantified analysis of a nutritional diary which the patient has kept a specified period of time, usually three days to one week⁽¹³⁾. Unfortunately, the time involved in such a procedure makes the undertaking rather unappealing to most primary contact health care providers. Instead most practitioners rely upon the premise that if a patient has the condition, chances are he is deficient in those nutrients which previous studies have shown are common to his group. As can be seen by the Kowsari and coworkers study, the list of those essential nutrients that can be deficient is quite large. This is the basis behind the recommendation of a low dose broad spectrum multivitamin/multimineral supplement to most sufferers of OA. This is probably satisfactory for those patients who are generally asymptomatic and whose degeneration is not rapidly progressing. Whether this is sufficient for the symptomatic patient or those with progressive OA is open to much debate, especially considering the information suggesting the use of larger doses of individual essential nutrients in these instances.

Joint Range Index	Clinical Status	Oral Dosage of Niacinamide/Day	Total mg Niacinamide taken/Day
96-100	No joint dysfunction		
86-95	Slight joint dysfunction	150-250 mg 6x (every 3 hrs.)	900-1500
71-85	Moderate joint dysfunction	250 mg 6x (every 3 hrs.) or 250 mg 8x (every 2hrs.)	1500-2000
56-70	Severe joint dysfunction	250mg 8x (every 2 hrs.) or 250 mg 10x (every 1.5 hrs.)	2000-2500
55 or less	Extremely severe joint dysfunction	250 mg 10x (every 1.5 hrs.) or 250 mg 16x (every hr.)	2500-4000

Table 1. Niacinamide Supplementation for Joint Dysfunction (adapted from Kaufman with permission, 1955)

Vitamins

Vitamin B₃ or Niacin was claimed to improve joint mobility by Kaufman^(14, 15) when doses far in excess of the US RDA were orally administered to those individuals who exhibited a decreased joint range index (JRI). Amounts taken varied from 900-4000 mg (US RDA approximately 17 mg) and were inversely related to the JRI (table 1). In every case the author claims to have measured an improvement. This improvement was not enhanced by Vitamins C, A, D, B₁₂, riboflavin, thiamine, pyridoxine, or calcium pantothenate. However, this was not a randomized clinical trial, but a descriptive study. No placebo was used, and therefore neither the patients nor the researcher was "blinded". Also this study did not distinguish between those individuals with OA from those without it, it simply measured improved capacity for joint movement. It can only be assumed that this therapy would have a positive effect on OA since within the large population studied (n=663), some individuals aged 1 to 81 years with decreased mode of action was proposed for the supplementation except for the generalization that "it seems to induce metabolic changes in articular cartilage cells (chondrocytes) which enhance the ability of cartilage to repair itself and better fend off the adverse effects of joint wear and tear and again that when the patient subsists on diet alone." It is interesting to note however, that as long as the patients continued their large intake of niacinamide, their JRI remained very high. Once they discontinued therapy it fell back towards its initial level Kaufman⁽¹⁵⁾ used a number of long term case studies to illustrate this point.

Finally, it is important to note that the form of B₃ given to patients was niacinamide and not niacin or nicotinic acid. The latter substances often cause flushing, itching of the skin and gastric distress.

A deficiency of pantothenic acid has been shown to cause degenerative joint changes in rats⁽¹⁶⁾. This involved severe inhibition of chondrogenesis and endochondral ossification and it was hypothesized that there may be a link between pantothenic acid and arthritis. Since then Annand^(17,18) found variable improvement with osteoarthritis and pantothenic acid supplementation in a descriptive study (n=26) and Barton-Wright and Elliott⁽¹⁹⁾ have noticed decreased levels of pantothenic acid in the diets of OA patients when compared to US RDA's. However pantothenic acid in the form of calcium pantothenate was found to be non-effective by Wheatley and coworkers for improvement of OA signs and symptoms in a double blind randomized control test (20). In the 59 subjects observed, duration of morning stiffness, degree of disability, severity of pain, requirements of paracetamol, depression and ESR were measured over 2 months and no significant results were obtained when compared to a control group.

Vitamin C (ascorbic acid) has long been known to affect collagen formation by virtue of its participation in the hydroxylation of peptide-bound proline and lysine in collagen⁽²¹⁻²³⁾. Apparently hydroxyproline residues contribute to the stabilization of the triple helix formation of collagen, while hydroxylsine residues participate in intra- and intermolecular crosslinks. Initially the vitamin's function was thought to be to maintain iron in its required moiety—the reduced (ferrous) state. Later it was shown to regulate the activities of the two hydroxylases involved⁽²⁴⁻²⁶⁾ and stimulate polypeptide synthesis⁽²⁷⁾ as well.

Due to the avascular nature of cartilage, accessibility to nutrients is an apparent problem. Cartilage derives its nutrients mainly from synovial fluid produced by the synovium in the joint capsule⁽²⁸⁾. When the synovium is damaged as is the case with OA, normal synovial fluid production is ultimately reduced. This retards regeneration of the cartilage after damage. Increasing the amount of serum Vitamin C could play an important role in the joint degeneration - regeneration process and has been the subject of some animal based research.

With this in mind, Schwartz and coworkers⁽²⁹⁾ examined the cartilage of guinea pigs with experimentally induced OA. Disease development (cartilage erosion, structural deformation and eburnation) was more severe in animals maintained on 2 mg of dietary ascorbic acid per day (1mg/kg/day) while only slight fibrillation and some osteophyte formation was apparent in the animals maintained on the 150 mg/day vitamin C diet (75mg/kg/day). In comparison, a human being has a US RDA of approximately 1 mg/kg/day. In a later study, it was found that the type of collagen and the relative concentrations of each type did not change when the amount of dietary intake of vitamin C varied (scurbutogenic levels were not tested) but that the differences observed were apparently due to the overall gross amount of collagen produced⁽³⁰⁾.

The question as to what effect, if any, ascorbic acid has on articular chondrocyte DNA synthesis (a measure of cell mitosis) was addressed by Krystal, Morris and Sokoloff⁽³¹⁾. Traditionally it was thought that mature articular chondrocytes were incapable of mitotic division, hence the very slow repair process of damaged articular cartilage. Krystal and coworkers were able to show that in both human and rabbit articular cartilage explants DNA synthesis was promoted by increasing amounts (.05-.2mM) of vitamin C (normal blood values: .01-.1mM). This occurred up to a maximum concentration (.8mM), after which cell death ensued, presumably due to toxicity caused by the ascorbic acid. Two other factors which further increased DNA synthesis were the addition of a proteolytic

enzyme (trypsin or collagenase) and in the case of human cartilage explant, fresh human serum. This suggests that steric hindrance, removed by liberation of the cells from the collagen and proteoglycan matrix in cartilage, is a potent inhibiting factor. It also suggests that there are blood borne substances which affect cell division as well. Nevertheless the authors found that while the effects of ascorbic acid, proteolytic enzymes and human serum worked synergistically, there actually were 3 separate mechanisms involved and a limitation of any of the three had a profound influence on DNA synthesis.

In a similar study, Prins, Liman, McDevitt and Sokoloff⁽³²⁾ showed that Vitamin C (.2mM) could also increase glycosaminoglycan (GAG) synthesis of rabbit articular chondrocytes in vitro. GAG's are a subunit of the proteoglycan molecule found in the background matrix in collagen and are instrumental in giving cartilage some of its unique properties. The stimulation by Vitamin C of proteoglycan production was superior to any of the peptide growth factors used to stimulate GAG synthesis. Thus the background matrix production of cartilage is significantly enhanced by the presence of ascorbic acid and adequate amounts in the diet are critical in order for this to occur.

It seems the next question then to be addressed concerning vitamin C is, "What is the optimum amount for patients with a degenerating joint?" To the author's knowledge this has yet to have been answered successfully, but based on the experiments previously mentioned one might assume it is in excess of the US RDA (60mg.).

Some beneficial effects on experimentally induced inflammation in experimental animals have been reported⁽³³⁾ for vitamin E, but the precise mechanism is unknown. It is hypothesized that it has to do with maintenance of the lysosomal membrane so an inhibition of chemical mediators which enhances inflammation occurs. Certainly a decrease in the amount of inflammation should be associated with a decrease in the amount of pain in a joint. This could explain the findings of a study surrounding alpha-tocopherol, the most biologically active form of Vitamin E. It was found to be highly significant for relief of pain in a randomized clinical trial performed by Machtey and Ouaknine⁽³⁴⁾. In their study of 29 patients (average age 56.5) with various forms of symptomatic Osteoarthritis (average duration of symptoms 9.3 years), 51% claimed to have significant improvement on a daily record chart over 10 days of treatment (600mg/day) (US RDA 8-10 mg). Amounts of analgesics taken by the patients were recorded as well, and of the eight patients that did so, 5 belonged to the group which did not improve while taking vitamin E, and 2 others performed (ESR, complete blood count, and blood concentrations of urea, uric acid, creatinine, alkaline phosphatase and transaminase) before and after the trial and these findings were unchanged. Also, no side effects were reported.

Concerning tissue regeneration Packer and Smith⁽³⁵⁾ have shown that the addition of vitamin E to fibroblasts in a cultured medium greatly increases their life-span. This may explain the positive effects vitamin E has on wound healing, and suggests further use in osteoarthritis studies. As before thought, to date none have been reported.

Vitamin D (cholecalciferol) deficiency was thought to possibly contribute to the osteoarthritic process by causing a decreased uptake of calcium from the gut. This might subsequently cause decreased mineralization of bone and hence weaken it. Bird, Wright, Hennes and Theiss⁽³⁶⁾ found however that there was no significant difference in serum levels of OA patients when compared to normal values. This suggests that vitamin D probably does not play a causative role in the pathogenesis of osteo-arthritis.

The necessity of Vitamin A (retinol) in the process of cell differentiation and maturation has long been known⁽³⁹⁾. Whether this impacts on OA has not been studied to date. It is interesting to note however that in a recent study on patients with OA, synovial fluid values of retinol and retinol binding protein were 40% of normal serum values, which is what they should mirror⁽⁴⁰⁾. This is significant since nourishment of cartilage chondrocytes stems from the synovial fluid⁽⁴¹⁾ and a decrease here could affect the maturing chondrocyte. Retinol may thus be implicated as playing a causative role in the inability of the cartilage to regenerate well once injured, but further studies are needed.

Minerals

There has been very little research performed on the role of minerals in the osteoarthritic patient. While altered copper metabolism in Wilson's disease has been associated with premature degenerative arthritis at the knees⁽⁴²⁾, copper and ceruloplasmin levels are not significantly altered in OA⁽⁴³⁾. This is contrary to the findings in inflammatory arthritides like rheumatoid arthritis in which copper and ceruloplasmin serum values are elevated. However, OA being generally non-inflammatory is not affected as such and overall is probably not impacted significantly by copper in the diet.

Increased deposition of calcium, magnesium and phosphorus have been noted in osteoarthritic cartilage⁽⁴⁴⁾ but the dietary implications of this are unknown. While this biochemical alteration probably affects the hydration of cartilage and precipitates some of the degenerative changes, there is no evidence to date to suggest that diet plays any role in the etiology of the biochemical changes.

Sulfur is the only other mineral which has been investigated in association with OA. This mineral is part of the GAG side chain molecules keratin sulphate and chondroitin sulfate. The sulfur used in all of the studies was an extract taken from a known source of glycosaminoglycans. While collagen and proteoglycan synthesis in cartilage increases up to five times its normal rate in the early stages of OA⁽⁴⁵⁾, overall proteoglycan content is decreased^(41,42).

Specifically keratin sulfate is depleted⁽⁴³⁾ While there is a decrease in the chondroitin sulfate chain length⁽⁴⁶⁾. Bollet⁽⁴⁴⁾ found that commercial preparation of calf cartilage extract plus bone marrow labeled with ³⁵S showed increased incorporation into chondroitin sulfate of young rat costal cartilage as well as in elderly human osteoarthritic cartilage (any effect on keratin sulfate was not able to be determined). However this does not prove an increased rate of synthesis or deposition for the human GAGs, but merely that this form of supplementation makes sulfur available for use by the body.

The effects of bovine tracheal cartilage injected subcutaneously were assessed in a pilot study by Prudden and Balassa⁽⁴⁵⁾ and found to be excellent or good for pain and functional disability in 25 out of 28 cases studied. The major physiological effect in this study was thought to be in reducing inflammation. They also hypothesized that the effects observed in OA patients might be due to a reconstitution of the affected cartilage by furnishing biochemical components that could be utilized in resynthesis. Unfortunately no follow up studies were ever performed.

Extracts of the green lipped mussel, *Perna canaliculus*, were found to be an effective supplement or possible alternative to orthodox therapy in the treatment of osteoarthritis⁽⁴⁶⁾. In this study, 15 out of 33 people who finished the program had significant results for improvement with pain, limbering up time, and joint function. Werbach suggests that the effects were probably due to high concentrations of GAG's, particularly chondroitin sulfate⁽⁴⁷⁾.

Conclusion

In reviewing the literature it is apparent how far behind research

in nutrition is when compared with other approaches in the treatment of osteoarthritis. A simple scan of any recent edition Index Medicus will show that drug studies on OA are performed at least 25 times more often than nutritional studies. This observation flies in the face of logic. By definition essential nutrients are those substances which are needed for growth and normal function in which cannot be synthesized by the human body⁽⁴⁸⁾. These are substances which have already been proven to have biological activity absolutely necessary for health life. Pharmacological agents, on the other hand, are not only nonessential, but seldom address the biochemical events of the osteoarthritic process. Yet essential nutrients, these naturally occurring vital agents, are generally being ignored by researchers in favor of pharmacological or physical therapeutics. This seems simply to be a result of politics and the pocketbook. Many substances such as vitamin C, vitamin A, vitamin E, niacin and sulfur have shown promising results in initial studies with osteoarthritis. However much, much more work remains before even these can be confidently recommended by the doctor of a patient with OA in levels above the RDA.

In conclusion, the prospects for dietary changes as an aid in altering the course and effects of osteoarthritis are good. There is little question that proper weight control will positively influence the course of osteoarthritis of some joints. When it comes to the role of non-caloric essential nutrients the impact is less clear. Certainly more human studies need to be performed. And until these are performed any clinical recommendations for vitamin and mineral supplementation by OA patients significantly above the US RDA should remain guarded.

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