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Acupuncture for Fibromyalgia

By Nassim Assefi, MD

In one peer-reviewed study, at least 22% of patients with fibromyalgia (FM) had tried acupuncture in the past year.[1] The National Institutes of Health Consensus Development Statement on Acupuncture states: "...musculoskeletal conditions such as fibromyalgia, myofascial pain, and epicondylitis, are conditions for which acupuncture may be beneficial."[2]

Although scientific studies are provocative, and acupuncture is widely regarded by the public as effective in alleviating chronic pain, its potential benefit in chronic conditions like FM is largely unknown.

Definition and Symptoms

Fibromyalgia is a disorder of unknown etiology that is characterized by diffuse musculoskeletal pain and a panoply of other chronic symptoms. In 1990, the American College of Rheumatology established the diagnostic criteria for FM: diffuse musculoskeletal pain for at least three months and the presence of at least 11 of 18 tender points on physical examination *(see Figure)*.[3]

Although not included in the case definition, many FM patients report symptoms such as sleep disturbance, fatigue, psychological distress, chronic headaches, irritable bowel, and interstitial cystitis.[4-6] Routine laboratory testing generally is normal.

Prevalence

Some sources estimate that 2% of the general population, or 6 million Americans, suffer from FM, making it the second most common rheumatologic condition after osteoarthritis. In both community and clinic settings, 85% of patients are women and many are middle-aged.[5,6]

Conventional Treatment

Most randomized, controlled trials of allopathic interventions have failed to demonstrate a sustained effect, although antidepressants (especially tricyclics), aerobic exercise, and cognitive behavioral therapy may provide some benefit. Thus, it is not surprising that 60-90% of patients with FM use complementary and alternative medicine (CAM).[7,8]

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Mechanism of Action

Acupuncture has been used as a therapeutic intervention for more than 2,500 years in China, and since its reintroduction in the United States in the early 1970s, it has become one of the most widely used and accepted forms of CAM.

Western biomedical theory cannot predict the effects of needling at acupoints; furthermore, no unique anatomic structures corresponding to such points have been found.[9] Of the structures examined, free nerve endings have the highest correspondence to acupuncture points.[10] Of relevance to FM, a large number of acupuncture points coincide with trigger points.[11]

A central mechanism of action has been suggested by a small study using single photon emission computed tomography that demonstrated baseline asymmetry and lower count ratios in the thalamus of pain patients compared to healthy volunteers.[12] Following acupuncture, the asymmetry resolved and most patients had substantially increased uptake of radiotracer in the brain stem.

Despite the absence of well-recognized anatomical sites of action, studies in animals and humans clearly have shown that acupuncture results in measurable biological changes, including release of endorphins and monoamines. Acupuncture analgesia is blocked by opioid antagonists such as naloxone,[13] and injections of antibodies against enkephalin, beta-endorphin, and dynorphin into analgesic regions of the central nervous system, but not elsewhere, block acupuncture analgesia.[14,15]

Clinical Trials

Literature searches of PubMed, Cochrane registry, CINDAHL, Biosis, Embase, and *Alternative Medicine Alert*, supplemented by conference abstracts, citations, and letters, using "acupuncture" and "fibromyalgia" or "fibrositis" or "fibromyositis" as key words revealed eight relevant studies.

Although all of these studies consistently have shown beneficial effects of acupuncture for fibromyalgia symptoms, the majority have been small, poorly controlled, non-randomized trials.

Two excellently designed randomized, controlled trials (RCTs) are the exception. The first is a three-week RCT of electroacupuncture in 70 patients.[16] Pain threshold improved significantly by 70% in the active intervention group compared with 4% in the sham group. In fact, seven of the eight outcome measures (pain threshold, number of analgesics used in last week, subjective and regional pain, sleep, morning stiffness, and patient- and physician-rated improvement) showed significant improvement with treatment; no changes in any of these parameters were encountered in the control patients. Furthermore, for five of the eight outcomes, there also were significant differences between the treated and untreated groups.

The second study randomized 60 patients to weekly acupuncture, weekly sham acupuncture, or usual care.[17] All patients received 25 mg of amitryptyline at bedtime and treatment lasted 16 weeks. Validated pain and depression scales were significantly different between the acupuncture group and the two control groups; no improvement occurred in the sham acupuncture and usual care groups.

Limitations of the above studies include the following: 1) there is considerable controversy over electroacupuncture and whether it is equivalent to conventional acupuncture (some practitioners believe that the former provides primarily short-term analgesia, while the latter may afford longer-term pain relief); 2) in neither study were measures used to assess if patients actually were blind to treatment; 3) the first study did not include functional or psychological measures, and the second study did not use any objective measures (such as dolorimetry or blinded assessment); and 4) there was no long-term follow-up on either study.

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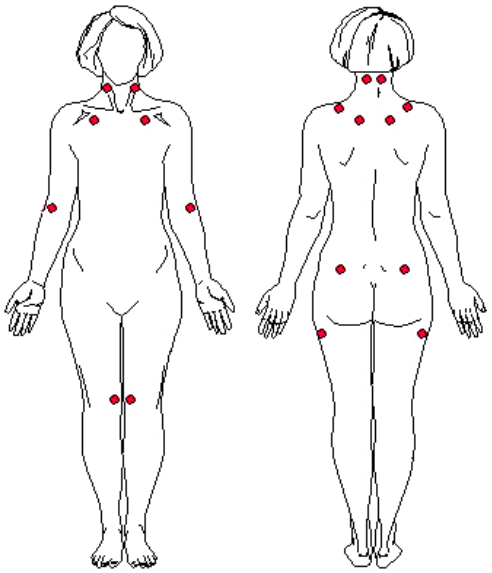
Figure

Fibromyalgia trigger points



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Long-term follow-up is crucial because FM is a chronic illness with symptoms that wax and wane over time and the analgesic effects of acupuncture may be transient, especially with brief treatment protocols (e.g., four weeks or less).

Methodological Challenges

Virtually all clinical trials of acupuncture have been plagued by serious methodological flaws *(see Table)*.

In addition, there are diverse schools and styles of acupuncture that likely vary in their efficacy for certain conditions; hence no single trial can claim to be representative of all types of acupuncture.

Perhaps the methodological issue posing the greatest difficulty in assessing the potential utility of acupuncture is the choice of controls. Invasive sham acupuncture consists of the insertion of needles at locations on the body supposedly ineffective for the condition being treated. However, there are no standards to guide researchers in identifying appropriate sham point locations, or depth, direction, or duration of needle insertion.

The use of sham controls depends heavily on traditional acupuncture theory that posits that acupuncture should be effective only if condition-specific classical points are used. Non-invasive sham acupuncture, which attempts to mimic an inert placebo, uses non-insertive needling devices to simulate the sensation of acupuncture. However, patients must be blindfolded, acupuncture naïve, and assessed for expectation and credibility of treatment group in order to maximize successful blinding.

Table 2

Methodological challenges of acupuncture studies[18,19]

- Appropriate and adequate treatment (a sufficient number of points stimulated per treatment, adequate frequency and duration, adding extra stimulation of acupoints using electroacupuncture or moxibustion, and fixed regimens stimulating predetermined acupoints vs. individualized treatments);
- Appropriate comparison groups;
- Blinding of patients and practitioners (although the latter of which is impossible, but assessors blinded to treatment group can be used for objective measures);
- Adequate sample sizes;
- Adequate assessment of outcomes (validated subjective and objective measures); and
- Adequate duration of trial and follow-up.

Adverse Effects

Overall, acupuncture is extremely safe and major injuries are uncommon. A study compiling Medline-reported acupuncture complications between 1981 and 1994 revealed adverse events in only 193 patients worldwide and three reported deaths.[20] Hepatitis was the most common infectious complication, reported in 100 of the 193 patients. This occurred when sterilization of the acupuncture needles had not been performed properly. Pneumothorax was the second most common complication, reported in 23 patients. Patients with chronic obstructive pulmonary disease were at highest risk. Other minor complications included the "acupuncture faint" (a vasovagal reaction), bleeding, localized skin infection, and localized pain.

Most of the serious complications can be avoided in the United States, where sterile, disposable acupuncture needles are used and needle penetration tends to be less deep than in classical Chinese acupuncture.

Conclusion

Two well-designed but small RCTs of acupuncture for the treatment of FM provide promise of a beneficial therapeutic intervention in a condition that currently has few effective treatment options and is associated with substantial disability.

Although the exact mechanism of acupuncture analgesia is not understood, numerous studies demonstrate

shifts in neurohormonal concentrations following acupuncture that make chronic pain relief biologically plausible. The effects of invasive sham acupuncture and placebo acupuncture, while conceived of as controls for true acupuncture, are largely unknown. Nevertheless, acupuncture has few risks other than the out-of-pocket expenses incurred by patients whose insurance plans may not cover acupuncture treatments.

Many questions will be answered by two ongoing National Center for Complementary and Alternative Medicine-sponsored RCTs that are larger than previous studies and have addressed many of the methodological flaws of the past; results are due by 2003.

Recommendation

Although there is no consensus regarding optimal treatment for FM, acupuncture should be considered in conjunction with antidepressants, aerobic exercise, and cognitive behavioral therapy. However, specific recommendations such as type of acupuncture employed, the duration and frequency of treatment, and the degree of acupoint stimulation cannot be made definitively. ❖

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Inositol as a Cholesterol-Lowering Agent

By Georges Ramalanjaona, MD, DSc, FACEP, MBA

CORONARY HEART DISEASE (CHD) IS THE LEADING cause of death in Western countries, yet its prevalence is low in Japan and developing countries. Primary

and secondary prevention clinical trials in persons with elevated cholesterol levels have shown that reducing serum cholesterol levels by diet alone or diet plus drugs results in reduced CHD morbidity and mortality.[1] Since the positive association between serum cholesterol level and risk of CHD is well established, it is proposed that dietary fiber may influence the etiology of CHD due to its cholesterol-lowering property.

Inositol or phytic acid (PA), a natural compound found in fiber (seeds and cereal grains), may play a significant role in reducing serum cholesterol by decreasing the zinc:copper ratio.[2] A high ratio is associated with hypercholesterolemia.

There is increasing evidence that consumption of non-fermented soy protein, which contains PA, in place of animal protein may lower serum cholesterol levels.

Pharmacokinetics

PA (or myo-inositol hexaphosphate) is a major phosphorus compound. In plants, PA accounts for 70% of the phosphate content and contributes between 1% and 7% of dry weight.

PA has an antinutrient property. It chelates with multivalent cations, such as zinc, calcium, and iron, to form PA-insoluble complexes that are eliminated in the stool, thus reducing the bioavailability of minerals. This inhibitory effect of phytate depends on the degree of phosphorylation of inositol: The higher the degree of phosphorylation, the more significant is the inhibition of cation absorption.

Mechanism of Action

PA has a strong chelating property with minerals. It may have a beneficial effect in lowering serum cholesterol levels by preferential binding of PA to zinc, which results in a decreased zinc:copper ratio.[3,4]

PA also is considered a natural antioxidant because it inhibits iron-catalyzed hydroxyl radical formation and lipid peroxidation. PA that is endogenous to food may protect against free radical formation within the food and may decrease free radical formation in ingested food in the gastrointestinal tract.[5]

PA also has been reported to protect against ischemic heart reperfusion injury by chelating iron, eliminating free radical formation, and subsequent lipid peroxidation in vitro.[6]

Using a rat model, Jariwalla demonstrated the effects of the addition of a natural phytate salt (IP6) on serum lipid and mineral levels in animals fed a cholesterol-enriched and standard diet.[1,2] Results showed a significant lowering of serum total cholesterol by IP6 both in animals fed a cholesterol-enriched and standard diet, but a reduction of the zinc:copper ratio only in the cholesterol-enriched group at 11 weeks.

Clinical Studies

To date, there are only limited clinical trials that have studied the effectiveness of PA in reducing serum cholesterol levels in humans.[7,8]

Dormer and Fisher examined the long-term effects of a widely used form of inositol called inositol hexaniacinate (IHN) on 16 patients who were treated with 400 mg of IHN three times daily for one month, followed by 400 mg four times daily for a total of 40 weeks.[8] They reported a statistically significant reduction of serum total cholesterol ($P < 0.05$) using the pre- and post-treatment analysis (evidence grade I) during the 40 weeks of therapy.

Another trial by Hutt used a sequential control design (evidence grade II) to study the effectiveness of a combination of 900 mg of inositol nicotinate and 1.5 g of Clofibrate daily in 19 patients with hypercholesterolemia during a period of 24 weeks.[7] The author reported a statistically significant lowering of low-density lipoprotein (LDL)-cholesterol type IIb ($P < 0.05$) and an increase of all three types of high-density lipoprotein-cholesterol.

Recently, Anderson et al summarized indirect but strong evidence of the effects of PA in lowering both total and LDL-cholesterol levels using a meta-analysis of 38 controlled clinical trials (evidence grade I).[9] They concluded that daily soy protein of 25-50 g (which contained PA and was substituted for animal protein in subjects with higher baseline cholesterol levels), resulted in a 9.3% and 12.9% decrease in total and LDL-cholesterol values, respectively. This hypocholesterolemic benefit of soy was in addition to the effect seen with a diet low in saturated fat and cholesterol.

Several components of soy protein have been implicated in lowering cholesterol levels: PA, isoflavones, and saponins. Although there is an apparent synergy among these components in providing hypocholesterolemic benefit, the exact role of each component and the composition of the soy were not reported in earlier clinical trials.

On-Going Clinical Research

On-going clinical trials in the United States and abroad are testing the nutritional effects of a special corn, which was patented by Victor Raboy in 1997. The corn is low in PA and high in inorganic phosphorus (thus readily absorbable). Clinical trials will examine the effect of the corn on zinc, iron, and calcium absorption, which ultimately affects serum cholesterol in humans.[10]

These therapeutic trials will continue until statistically significant results are achieved.

Contraindications and Precautions

Diets high in PA may exacerbate malabsorption problems in patients with irritable bowel syndrome and celiac disease. PA supplementation is not recommended in these populations.

Due to its inhibitory effects on minerals, PA consumption should be decreased in people with high calcium or iron requirements (children and pregnant woman) or with low calcium or iron intakes.[11]

Dosage

Virtually all published clinical trials have used purified PA or dietary PA that is isolated from or a component of a natural product (including seeds, whole grains, and cereals) and comprises between 1% and 7% of the product's dry weight.[11]

The oral dose of inositol in its inositol hexaniacinate form is 400 mg three to four times daily.[12]

Recently, the Food and Drug Administration approved labeling health claims that daily consumption of 25 g of soy protein has a hypocholesterolemic effect as part of a diet low in saturated fat and cholesterol, which may reduce the risk of heart disease.[13,14]

Conclusion

Current conclusions are derived mainly from in vitro, animal, and epidemiological studies.

Based on these available preliminary data, PA appears to be a safe and effective agent in lowering serum total cholesterol levels. PA could be studied as a reasonable addition to the standard, cholesterol-lowering diet. However, results from human trials studying the effects of dietary PA in preventing heart disease are lacking.

Recommendation

At this time, there is insufficient, direct evidence to recommend PA as a complementary, secondary preventive agent for lowering serum total cholesterol.

PA should not be given to patients with elevated cholesterol levels who have low or marginal zinc, iron, or calcium levels or intakes. ❖

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Boron Supplementation for Low Bone Density and Osteoarthritis

By Sharon L. Kolasinski, MD, FACP, FACR

ALTHOUGH THE BENEFITS OF CALCIUM SUPPLEMENTATION are well known and accepted by physicians

and the public alike, a variety of additives to calcium supplements have appeared in the marketplace that have less clear indications for general use. In search of better bone health, consumers must choose among supplements with added vitamin D, magnesium, glucosamine, and other ingredients. The consumer is now faced with yet another choice: Should she buy calcium supplements with or without boron?

In nature, boron is found in fruits, vegetables, legumes, and nuts. Boron also presents as a naturally occurring trace element in human bone. Bone matrix is composed of 90% type I collagen fibers and 10% noncollagenous proteins. The degree of mineralization of the bone depends on its location: Up to 90% of cortical bone is calcified, whereas only about 25% of spongy or trabecular bone is calcified. Trace elements include boron, as well as zinc, manganese, magnesium, and aluminum. These elements are present in both the mineralized and non-mineralized portions of bone, and their role in normal bone functioning, as well as in disease states, is not completely understood. Boron may have numerous and interdependent effects on hormone levels and bone metabolism.

Pharmacokinetics

Boron is readily and completely absorbed on oral administration.[1] It is rapidly distributed throughout the body water and the concentration in blood and soft tissue is the same, whereas the relative concentration in bone, nails, and hair is relatively increased. One widely quoted observation is that an increase in oral boron intake does not lead to a similar rise in plasma boron concentration.[2] Rather, a marked increase in urinary boron will accompany an increase in oral intake, suggesting the presence of a renal homeostatic mechanism.

Unlike many other minerals, boron is water-soluble. Boron is not metabolized and over 90% is excreted unchanged in the urine with a half-life of 21 hours. Because there are no useful serum markers of biological activity of boron, urine levels have been used as an outcome measure of boron supplementation. However, two findings make interpretation of urinary excretion data difficult. First, healthy volunteers may vary 10-fold in the amount of daily boron excretion. In addition, it is unknown whether the amount of boron excreted correlates with physiologic effects.[3]

Metabolism

Boron metabolism is intertwined with that of other minerals, including calcium, copper, magnesium, and phosphorus. The literature in animals, as well as in humans, addressing the role of boron in bone metabolism is both complex and confusing as a result. Animal data have suggested that phosphorus and magnesium levels in laboratory animals may be adversely affected if boron deficiency occurs. Calcium levels have been shown to vary with boron levels when potassium is manipulated in the diet.[4]

Physiology

The physiologic effect of boron is unknown. Characteristics of a boron deficiency state in humans have not been described. In blood, boron combines with hydroxyl groups and is known to form complexes with organic compounds containing hydroxyl groups in favorable positions. Identified interactions include those with serine proteases, nicotinamide adenine dinucleotide, pyridoxine, riboflavin, glycoproteins, and polysaccharides.[5]

Non-Medical Uses

Urban dwellers may be familiar with boron as the active ingredient in a number of roach-killing products. In fact, the Australian government issued a regulation that cited boron as a poison, substantially reducing sales of boron supplements for a time.[6]

Bone Mineral Density

Many clinical trials manipulate multiple mineral levels within a single study. Some authors suggest that this type of experimental design more closely models conditions of nutritional stress.[4] However, it is unclear how the manipulated levels of minerals relate to variations in human diets or to disease states and their potential treatments.

In healthy subjects, boron levels may vary with age, nutrition, hormonal status, or other factors. Work by one group suggested an important relationship between boron levels and excretion of calcium and magnesium.[7] Eleven postmenopausal women with an average age of 61 years lived in a metabolic unit for 167 days. They were fed a low-boron diet at baseline and were supplemented with 3 mg of boron daily for 24 days. They appeared to have a dramatic reduction in calcium and magnesium urinary excretion. The authors suggested that boron might have an important role in the treatment of postmenopausal osteoporosis since boron supplementation might reduce loss of calcium in the urine.

A more complete reporting of data on this original group of 11 women was published a decade later.[2] It was noted that the effect of boron on calcium excretion, and other effects, was dependent upon magnesium. In fact, urinary excretion of calcium was increased in the presence of boron supplementation when magnesium supplementation was given as well. Boron supplementation

led to narrowing of the QRS complex in the absence of magnesium supplementation and was associated with an increase in systolic and diastolic blood pressure, regardless of magnesium supplementation. Neither effect took participants out of the normal range.

A study by a different group of investigators failed to demonstrate a correlation between boron supplementation and reduced mineral excretion.[8] In this study, healthy sedentary and athletic college women received 3 mg/d of boron and were followed for 10 months. Although the small size of the study (26 subjects) limits its power, the authors could not demonstrate any significant correlation between boron and excretion of calcium, phosphorus, or magnesium. Serum levels of phosphorus were lower and serum levels of magnesium were higher in those supplemented with boron, but they also were influenced by exercise. This widely cited study has added to the appreciation that the role of boron in the body is likely to be related to numerous other factors.

Hormones, Osteoporosis, and Menopause

In addition to the suggestion that boron levels may vary with hormonal status, boron itself may alter hormone production. Neilsen and colleagues showed in their early work that boron supplementation could result in increased 17 β-estradiol and testosterone levels in postmenopausal women.[7] In a study of seven healthy male volunteers with an average age of 26 years, boron supplementation of 10 mg daily for four weeks also was associated with a significant increase in plasma estradiol levels.[2] However, in these young men, there was no significant change in testosterone levels. The authors suggested that boron may be of cardiovascular benefit in young men, but no data were supplied to support this contention. Whether boron may exert effects on bone mineral density as a result of effects on estrogen levels has not yet been explored. No studies have yet followed actual bone mineral density measurements to assess a direct effect of boron supplementation on clinically significant osteoporosis.

A corollary of the supposition that boron has important interactions with estrogen levels is the suggestion that it be used to treat perimenopausal symptoms. One group followed electroencephalograms (EEG) and tests of cognitive, spatial, and psychomotor functioning in subjects on boron. Several experiments were performed and each involved a small number of participants, including postmenopausal women who varied with respect to whether they took hormone replacement therapy. EEG findings were consistent with what had been found in animals: Low boron intake (< 0.3 mg/d) was associated with EEG patterns suggestive of drowsiness and low mental alertness. Low boron intake consistently was associated with a reduction in memory and attention on psychological testing.[9]

An additional trial specifically looked at boron's effects of the functioning of perimenopausal women. Forty-six women participated in this double-blind, crossover trial in which all women took boron supplementation of 3 mg/d as sodium tetraborate at some point in the trial. Subjects completed daily symptom checklists. Boron supplementation was associated with an increase in vasomotor symptoms, sleep disturbance, and total symptoms (including depression, anxiety, and somatic symptoms).[10]

Osteoarthritis

One study has shown that boron levels, along with those of lead and zinc, were reduced in patients with osteoarthritis of the hip when those patients went for hip replacement.[11] Surgical specimens of femoral heads revealed an overall reduction in mineralization, which researchers speculated reflected increased bone turnover that is part of the osteoarthritic disease process. Interestingly, the level of demineralization in the osteoarthritis patients was greater than in a group of patients who were undergoing hip replacement due to fractures of the femoral neck.

Some have speculated that boron might be a useful supplement for patients with osteoarthritis.[12] Although boron may be reduced in certain disease states, it is less clear that boron supplementation will alter the risk or severity of arthritis. The only study to address the question found no significant difference between a group of osteoarthritis patients given 6 mg daily of boron as sodium tetraborate for eight weeks and a group given placebo. Although the study was double-blind and placebo-controlled, only 20 patients were enrolled and a quarter dropped out due to lack of efficacy.[13] Outcome measures used were subjective and did not include standard benchmarks of improvement used in osteoarthritis research.

Adverse Effects

Boron toxicity results in behavioral depression, hypotonicity, ataxia, poor motor control, impaired operant learning of avoidance tasks, and drowsiness.[9] In addition, boron toxicity adversely affects fertility.[14] More severe intoxication may result in restlessness, tremor, confusion, and seizures.

Formulation and Dosage

Boron generally is not available as an individual supplement, but is an ingredient in some multivitamins and

calcium preparations. In the combination products, the dosage of boron generally is 1 or 2 mg per tablet.

The minimum daily requirement for boron has not been established.

Conclusion

The exact physiologic role of boron is not clear. It may affect bone metabolism, especially in conjunction with other minerals and vitamin D, with which it appears to have complex, interdependent relationships. It may modulate sex hormone production in men and women, alter cognitive function, and provide analgesia for arthritis sufferers, but data are preliminary at best in all of these areas of clinical application. Toxicity includes adverse central nervous system and reproductive effects.

Recommendation

Boron supplementation cannot be recommended on the basis of current research. Its basic role in metabolism of bone and the reproductive system remains unclear, as do its possible preventive or therapeutic uses. Considerably more research needs to be done to establish its role in health and disease. ❖

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CME Questions

8. Which of the following is *not* true regarding fibromyalgia?

a. Diagnosis requires at least three months of widespread pain.
b. More men are afflicted than women.
c. Diagnosis requires the presence of 11 of 18 tender points.
d. Fibromyalgia often is associated with other chronic symptoms such as sleep disturbance and depression.

9. Acupuncture is challenging to study in randomized, blinded, placebo-controlled trials because:

a. it is virtually impossible to blind the acupuncturist to the type of treatment received.
b. there is little consensus on what constitutes a sham acupoint.
c. placebo acupuncture needles are difficult to design.
d. All of the above are true

10. Many of the adverse effects of acupuncture can be avoided in the United States because:

a. the use of sterile, disposable needles sharply reduces transmission of infectious diseases.
b. depth of needle penetration generally is more extensive in U.S.-styled acupuncture.
c. acupoints are more likely to be stimulated by electroacupuncture and moxibustion.
d. U.S.-based acupuncturists receive more years of training.

11. Phytic acid (PA) plays a significant role in reducing serum cholesterol levels by:
a. increasing the zinc:copper ratio.
b. decreasing the zinc:copper ratio.
c. decreasing the zinc:iron ratio.
d. increasing the zinc:iron ratio.

12. Recently, the FDA has ruled that daily consumption of soy protein (which contains PA) at what dosage has hypocholesterolemic effect?
a. 5 g
b. 10 g
c. 25 g
d. 50 g

13. Anderson's meta-analysis of 38 clinical trials has summarized the effect of PA in lowering which type(s) of serum cholesterol?
a. Total cholesterol
b. Total cholesterol and LDL-Type IIb cholesterol
c. Both total and LDL cholesterols
d. Total, LDL, and HDL cholesterols

14. In healthy subjects, boron levels may vary with:
a. age.
b. nutrition.
c. hormonal status.
d. All of the above

15. Boron toxicity is characterized by:
a. drowsiness.
b. ataxia.
c. behavioral depression.
d. All of the above

Reader Comment

Comment: With regard to your July 2001 glucosamine article, I would like to bring three points to your attention. First, the claim that glucosamine can increase proteoglycan synthesis comes from old abstracts of in vitro work that were never published in article form. It has never been proven in the human model that glucosamine can increase proteoglycan synthesis, rather it likely prevents further breakdown by supporting and strengthening the existing cartilage. Secondly, a common misconception—that glucosamine is a well known and effective analgesic—was included. Glucosamine works as an analgesic (with chronic use) by supporting cartilage and the extracellular matrix. Lastly, I feel it is important to point out that the Reginster study showed 1,500 mg once daily to be as efficacious and well-tolerated as 500 mg tid, an important finding for patients who cannot follow three-times daily dosing.

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Response: *We do not know what oral glucosamine does in vivo in human cartilage; Dr. Tsourounis' speculations in this regard are no more conclusively proven than the data cited in the article. Her hypothesis about why glucosamine works as an analgesic is interesting, but there are no data to support it. Interestingly, we do not even know why there is pain in osteoarthritis. Finally, the Reginster study did not compare a once-daily dose to a three-times daily dose; they used only a once-daily dose vs. placebo. No comparison of tolerability or efficacy was made.*

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With Comments from John La Puma, MD, FACP

Age-Related Macular Degeneration and Antioxidants

Source: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS reports no. 8. *Arch Ophthalmol* 2001;119:1417-1436.

OBSERVATIONAL AND EXPERIMENTAL data suggest that antioxidant and/or zinc supplements may delay progression of age-related macular degeneration (AMD) and vision loss.

To evaluate the effect of high-dose vitamins C and E, beta carotene, and zinc supplements on AMD progression and visual acuity, the Age-Related Eye Disease Study (AREDS), an 11-center, double-blind clinical trial, enrolled participants if they had extensive small drusen, intermediate drusen, large drusen, non-central geographic atrophy, or pigment abnormalities in one or both eyes, or advanced AMD or vision loss due to AMD in one eye. At least one eye had best-corrected visual acuity of 20/32 or better. Participants were randomly assigned to receive daily oral tablets containing: 1) antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg); 2) zinc, 80 mg, as zinc oxide and copper, 2 mg, as cupric oxide; 3) antioxidants plus zinc; or 4) placebo. Supplements were taken in divided doses with food.

Outcomes included photographic assessment of progression to or treatment for advanced AMD and at least moderate visual acuity loss from baseline (≥ 15 letters). Primary analyses used repeated-measures logistic regression with a significance level of 0.01, unadjusted for covariates. Serum level measurements, medical histories, and mortality rates were used for safety monitoring.

Average follow-up of the 3,640 participants, ages 55-80 years, was 6.3 years; 2.4% were lost to follow-up. Fifty-six percent of the participants were female, 96% were white, and the median age was 69 years. Comparison with placebo demonstrated a statistically significant odds reduction for the development of advanced AMD with antioxidants plus zinc (odds ratio [OR], 0.72; 99% confidence interval [CI], 0.52-0.98). The ORs for zinc alone and antioxidants alone were 0.75 (99% CI, 0.55-1.03) and 0.80 (99% CI, 0.59-1.09), respectively. Participants with extensive small drusen, non-extensive intermediate size drusen, or pigment abnormalities had only a 1.3% five-year probability of progression to advanced AMD. Odds reduction estimates increased when these 1,063 participants were excluded (antioxidants plus zinc: OR 0.66, 99% CI, 0.47-0.91; zinc: OR 0.71, 99% CI, 0.52-0.99; antioxidants: OR 0.76, 99% CI, 0.55-1.05). Both zinc and antioxidants plus zinc significantly reduced the odds of developing advanced AMD in this higher-risk group. The only statistically significant reduction in rates of at least moderate visual acuity loss occurred in the antioxidants plus zinc group (OR 0.73, 99% CI, 0.54-0.99). No statistically significant serious adverse effect was associated with any of the formulations.

These data show that persons older than age 55 should have dilated eye examinations to determine their risk of developing advanced AMD. Those with extensive intermediate size drusen, at least one large druse, non-central geographic atrophy in one or both eyes, or advanced AMD or vision loss due to AMD in one eye, and without contraindications such as smoking, should consider taking a supplement of antioxidants plus zinc.

COMMENT

Acute macular degeneration is disturbingly common, genetically linked, and mysterious—its pathogenesis remains largely unknown. It is the leading cause of blindness in the United States among people age 65 and older.

More than 10 years ago, the National Eye Institute organized this large, multicenter study, and the data from it are invaluable. Due to the cost and focus on inexpensive supplements, it is unlikely to be repeated. With this major effort, the study has sufficient power to answer the question of whether AMD can be delayed and whether visual loss can be prevented or restored.

The study was very well designed and controlled. Patients could be enrolled with minimal or no drusen, or advanced, severe disease. Average follow-up was 6.3 years, and only a small percentage of patients were lost to follow-up.

In contrast to supplementation of beta carotene for stroke and heart disease, these results are very positive. Statistically significant reduction of moderate visual loss occurred in just one group of patients—those who took the antioxidant-zinc combinations. Many other outcomes trended toward significance, but did not reach the P = 0.01 level. Each individual supplement and the combination of supplements all appeared to slow progression of AMD, and all prevented progression to advanced AMD. The combination of all supplements was more effective than any one supplement by itself. One category of patients with AMD did not benefit—those with small drusen. All patients, of course, required ophthalmologic examinations for diagnosis and follow-up.

Whether to use beta carotene in smokers who have AMD, given the demonstrated increase in lung cancers, is a difficult, patient-by-patient decision. Arguably, another carotenoid, such as lutein or zeaxanthin, may be substituted. How long such supplementation should last and when it should be started are questions AREDS doesn't answer. Nor does it answer questions about long-term (> 10 years) toxicity, though no adverse effects were noted during the trial.

Recommendation

Patients who are at risk for or who already have AMD should take 500 mg vitamin C, 400 IU vitamin E, 80 mg zinc oxide, and 2 mg cupric oxide daily. Consider substituting another carotenoid for beta carotene in smokers. ❖

Cataract and Antioxidants

Source: A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. *Arch Ophthalmol* 2001;119: 1439-1452.

EXPERIMENTAL AND OBSERVATIONAL data suggest that micronutrients with antioxidant capabilities may retard the development of age-related cataract.

To evaluate the effect of a high-dose antioxidant formulation on the development and progression of age-related lens opacities and visual acuity loss, participants were randomly assigned to receive daily oral tablets containing antioxidants (vitamin C, 500 mg; vitamin E, 400 IU; and beta carotene, 15 mg) or no antioxidants. Participants with more than a few small drusen also were randomly assigned to receive tablets with or without zinc (80 mg of zinc oxide) and copper (2 mg of cupric oxide) as part of the age-related macular degeneration trial. Baseline and annual (starting at year 2) lens photographs were graded at a reading center for the severity of lens opacities using the Age-Related Eye Disease Study (AREDS) cataract grading scale.

Primary outcomes were an increase from baseline in nuclear, cortical, or posterior subcapsular opacity grades or cataract surgery, and at least moderate visual acuity loss from baseline (≥ 15 letters). Primary analyses used repeated-measures logistic regression with a statistical significance level of P = 0.01. Serum level measurements, medical histories, and mortality rates were used for safety monitoring.

Fifty-six percent of the participants were female, 96% were white, and the median age was 68 years. Of 4,757 participants enrolled, 4,629 (ages 55-80 years) had at least one natural lens present and were followed up for an average of 6.3 years. No statistically significant effect of the antioxidant formulation was seen on the development or progression of age-related lens opacities (odds ratio, 0.97, P = 0.55). There also was no statistically significant effect of treatment in reducing the risk of progression of any of the three lens opacity types or the need for cataract surgery. For the 1,117 participants with no age-related macular degeneration at baseline, no statistically significant difference was noted between treatment groups for at least moderate visual acuity loss. No statistically significant serious adverse effect was associated with treatment.

Use of a high-dose formulation of vitamin C, vitamin E, and beta carotene in a relatively well-nourished older adult cohort had no apparent effect on the seven-year risk of development or progression of age-related lens opacities or visual acuity loss.

COMMENT

In contrast to the study of age-related macular degeneration (AMD), but founded in part on the same theory (i.e., that cataract formation is an oxidative process that might respond to antioxidant supplementation), this study examined cataracts.

The methods, of course, were the same as in the AREDS study. One quarter of the total participants in the AREDS study were in this cataract prevention arm.

Beta carotene for smokers and former smokers was recognized as potentially injurious, and 117 (2.5% of all participants and 24% of the current smokers) of the participants stopped taking the study medications after being informed of the potential danger. Intention-to-treat analyses were performed on the original grouping.

Disappointingly, no change in visual effect, cataract (regardless of the type of opacity) development, cataract surgery, or other eye events was detected. The only adverse effect noted that was statistically significantly different than placebo was "yellow skin" (from the beta carotene).

As a side note, participants in the antioxidant treatment arms less frequently reported chest pains (19.8% vs. 22.8%, P = 0.01), and were hospitalized significantly less frequently for chest pain, abdominal pain, vasovagal episode, and fever. Conversely, the relative risk estimate of overall mortality among the antioxidant group is in the direction of harm (relative risk = 1.06; 99% confidence interval, 0.84-1.33), but was not significant.

It could be argued that AREDS studied the wrong antioxidants for this purpose—several prospective studies now associate benefit from lutein and zeaxanthin, carotenoids that are stored in the lens. But this information is presented with the benefit of hindsight.

Recommendation

Patients trying to prevent or treat cataract or avoid cataract surgery with supplementation of vitamins C, E, zinc, and beta carotene should be redirected. Those that want to continue should examine supplementation with lutein and zeaxanthin instead. ❖

In Future Issues:

Magnesium in the Treatment of Fibromyalgia

Vanadium for Diabetes Mellitus

Acupuncture for Addiction