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Glucosamine for Treatment of Osteoarthritis

By Sharon L. Kolasinski, MD, FACP, FACR

ALTHOUGH GLUCOSAMINE HAS BEEN USED CLINICALLY IN EUROPE since the 1960s, only recently has it become one of the most frequently taken dietary supplements in the United States. In vitro and animal studies performed decades ago in the United States resulted in little interest in this dietary supplement. Glucosamine gained popularity in this country only after the publication of *The Arthritis Cure* by Jason Theodosakis, MD, in 1997.[1] Since then, it has become one of the most commonly used supplements for osteoarthritis (OA).

Most adults age 40 and older experience some degenerative joint abnormalities and OA symptoms are present almost universally by age 75.[2] OA is a leading cause of pain and disability, including lost time from work. Current OA treatments provide only symptomatic relief and the traditionally prescribed nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with serious toxicities. Measures aimed at prevention or reversal of OA are not yet available.

OA results in loss of the articular surface. Cartilage loss reflects underlying biochemical, mechanical, and immunological changes, and particularly the loss of proteoglycan. As a naturally occurring building block of proteoglycan, glucosamine has received considerable attention in the treatment of OA. The best evidence indicates that glucosamine ameliorates OA pain as well as some NSAIDs with fewer short-term side effects, and can be considered for initial OA therapy along with appropriate lifestyle measures. Glucosamine also might be of benefit as adjunctive therapy for patients experiencing an incomplete response from current prescription OA medications.

Pharmacokinetics

Laboratory and animal studies show that more than 50% of glucosamine sulfate is non-ionized at the pH of the small intestine, which allows rapid absorption. In rats, 90% of glucosamine sulfate is absorbed and about 10% remains in the tissues. Autoradiographs demonstrate C^{14} in rat cartilage four hours after ingestion of C^{14}-labeled glucosamine.[3] Limited human studies have documented the absorption and metabolism of glucosamine. Six healthy volunteers

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ingested radiolabeled glucosamine—two orally, two intravenously, and two intramuscularly—and had serum radioisotope levels measured at various subsequent time points.[4] Absorption occurred rapidly; radiolabeled glucosamine could be identified in the serum as early as six hours after ingestion. Intramuscular administration resulted in higher serum concentrations than oral administration. Furthermore, radioactivity could be detected in the serum as late as five days later. Data are not available, however, to identify whether intact glucosamine is incorporated into human articular cartilage.

Mechanism of Action

Glucosamine is a normal component of virtually all human tissues. It is the principal component of O-linked and N-linked glycosaminoglycans, which form the extracellular matrix of connective tissue. An amino-monosaccharide, it is acetylated, and then becomes a building block of hyaluronan, keratan sulfate, and heparan sulfate.

In vitro studies have shown glucosamine affects chondrocyte gene expression and that addition of glucosamine to human chondrocyte culture leads to a dose-dependent increase in proteoglycan synthesis.[5,6] In the rabbit model, there has been a suggestion that glucosamine sulfate slows the progression of cartilage lesions.[7]

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Though glucosamine's effectiveness as an analgesic is well known, the mechanism by which that occurs still is unknown. Pain relief in OA may be related to an anti-inflammatory effect, but unlike NSAIDs, glucosamine has no effect on cyclooxygenase-dependent prostaglandin synthesis.[8]

Glucosamine may have several other mechanisms of action. In animal models of arthritis, glucosamine has been demonstrated to stabilize cell membranes, reduce the generation of oxygen-free radicals by macrophages, and inhibit lysosomal enzymes. Glucosamine may interact with cytokine-mediated pathways on chondrocytes or other inflammatory pathways as well. It may inhibit interleukin-1-induced nitric oxide activity, which mediates chondrocyte cell death. Glucosamine also may inhibit interleukin-1-induced increases in aggrecanase activity, which could lead to preservation of proteoglycan.[9,10]

Clinical Studies

Numerous short-term studies have suggested that glucosamine is effective in treating OA pain. Placebo-controlled trials have demonstrated short-term efficacy in terms of reduced pain, reduced stiffness, and increased range of motion. To identify how many patients might be expected to respond to glucosamine vs. placebo, a large, multicenter, randomized, double-blind, placebo-controlled trial (RDBPCT) was conducted.[11] In this study, 155 patients with symptomatic OA of the knee were randomized to either 400 mg/d of intramuscular glucosamine or placebo. Patients were followed for six weeks. The investigators found that 55% of patients taking glucosamine (compared with 33% in the placebo group) improved based on the Lesquesne index. This measurement instrument provides a composite score that takes into account pain, walking distance, and ability to carry out activities of daily living (ADLs).

In trials comparing glucosamine to NSAIDs, comparable efficacy in pain relief and functional improvement has been demonstrated. The analgesic effect of glucosamine, however, is delayed compared with that of NSAIDs and is longer lasting than that of NSAIDs after discontinuation of the treatment.[12-15] In one of the most frequently cited recent trials, 200 ambulatory patients with knee OA undergoing inpatient rehabilitation were randomized into two groups.[14] The double-blind design resulted in patients receiving either 1,500 mg/d glucosamine sulfate or 1,200 mg/d ibuprofen. After four weeks, both groups had improvements in pain and reduced limitations on ADLs. However, the glucosamine group achieved these improvements one to two weeks after the ibuprofen group. Side effects occurred in 35% of the ibuprofen group, but in only 6% of the glucosamine group.

A recent meta-analysis addressed some of the criticisms of studies to date, particularly criticisms of small size and short duration.[16] The authors surveyed the MEDLINE and Cochrane databases as well as other sources and identified six RDBPCTs comparing glucosamine to placebo. The meta-analysis also assessed a series of equally well-designed trials evaluating chondroitin sulfate. The investigators found that the trials showed moderate to large effects, but that interpretation was limited by inconsistencies in study methods and potential for bias from industry sponsorship. Nonetheless, the authors concluded that "overall, it seems probable that these compounds do have some efficacy in treating OA symptoms and that they are safe."

Considerable controversy persists about the chondroprotective effects of glucosamine. The most definitive study to date is a three-year Belgian radiographic study.[17] Two hundred twelve patients with OA were assigned randomly to receive either 500 mg oral glucosamine sulfate tid or placebo. Baseline and one- and three-year follow-up radiographs of the knees were compared. The data showed a mean joint space loss of 0.31 mm in the placebo-treated patients, but no cartilage loss in the patients on glucosamine sulfate. Symptomatically, patients in the glucosamine group improved in pain and physical function measures compared to baseline, while those in the placebo group worsened. Interestingly, though, symptom improvement did not correlate with radiographic findings. Radiographic progression in OA is known to be slow and variable.

This latter study has been criticized because the radiographic technique used is subject to variation in interpretation. However, it is the longest glucosamine trial to date and the safety profile for glucosamine did not differ from that of placebo. In particular, the authors noted that glucosamine did not affect annual fasting blood sugar levels.

Ongoing Clinical Research

A large, NIH-sponsored, multicenter trial is being carried out to address the unanswered questions about glucosamine and its possible role in chondroprotection. The placebo-controlled trial includes a glucosamine arm, a chondroitin arm, and a combination glucosamine-chondroitin arm, as well as an NSAID-treated group. It will be conducted over the next several years and a subset of subjects will be followed radiographically to help answer the remaining questions regarding prevention of OA progression. The study will enroll 1,500 subjects at 13 U.S. locations and will have a $12 million budget.

Formulation

In the United States, glucosamine often is sold in the hydrochloride form,[8] which is 99.1% pure and contains no sodium, unlike the sulfate form. In addition, the hydrochloride form provides 81.3% bioreactive glucosamine vs. 47.8% bioreactive glucosamine from the sulfate form. Thus, theoretically, about 860 mg of the hydrochloride form delivers the same amount of glucosamine as 1,500 mg of the sulfate form. It is not known if the sulfate moiety is essential to the action of glucosamine in OA. No head-to-head comparisons of the two types of glucosamine preparations have been published.

Adverse Effects

No serious adverse effects have been reported, though the longest published experience with glucosamine is three years.[17] Side effects related to long-term exposure are unknown. Many short-term glucosamine trials have reported a side effect profile indistinguishable from placebo. Some studies have made note of gastrointestinal complaints (nausea, vomiting, abdominal pain, change in bowel habits) and sleepiness.[15] Dropout rates in glucosamine groups generally have been low.

Contraindications and Precautions

Some authors have suggested exercising caution when recommending glucosamine to patients with diabetes mellitus.[18] Considerable in vitro and animal data suggest that glucosamine can enter the hexosamine biosynthetic pathway and cause insulin resistance. However, the clinical relevance of these observations and the risks of long-term glucosamine use by diabetics are unknown. Short-term studies in non-diabetic subjects have had equivocal results. One report on 10 healthy subjects showed that glucosamine did not affect insulin levels but did increase fasting plasma glucose levels.[19] A more recent study of 18 healthy subjects showed that glucosamine had no effect on insulin-induced glucose uptake.[20] The U.S. Food and Drug Administration web site for the Special Nutritionals Adverse Event Monitoring System (www.vm.cfsan.fda.gov) lists a case of hyperglycemia after glucosamine ingestion, but no details are provided. The three-year Belgian study included annual measurement of fasting glucose levels.[17] The authors reported, "there was no change in glycaemic homoeostasis, with fasting plasma glucose concentrations decreasing slightly in the glucosamine sulphate group." The ongoing NIH study is monitoring glucose levels repeatedly and should provide further information.

Patients with seafood allergies should avoid glucosamine, which is derived from chitin in crustacean shells. No case reports of cross-reactivity have been published.

Dosage

Virtually all published clinical trials have used oral glucosamine sulfate at a dose of 500 mg tid. As noted previously, however, many preparations available in health food stores and pharmacies are in the hydrochloride form. Because of its superior bioavailability, the hydrochloride form may require a lower dose to achieve the same efficacy, but this has not been demonstrated in pharmacokinetic or clinical studies. However, given that the sulfate form has been used in the bulk of available research, it seems reasonable to favor this preparation.

Conclusion

Glucosamine has been used to treat OA for more than 30 years. A large accumulated clinical experience and numerous positive, randomized, placebo-controlled trials have demonstrated the effectiveness of glucosamine preparations for relief of pain, stiffness, and functional disability caused by OA with a potency equivalent to that of NSAIDs. Based on generally short-term data, glucosamine appears to be substantially less toxic than NSAIDs and has been associated with only minor and infrequent side effects. Furthermore, meta-analyses have suggested efficacy as well, despite methodologic limitations to existing trials.

Recommendation

Glucosamine is a reasonable addition to the symptomatic OA treatment regimen that includes weight loss, exercise and physical modalities, and assistive devices as appropriate. Glucosamine might be used as an alternative to NSAIDs, especially for patients who are concerned about taking prescription medications or who have experienced adverse effects—including gastrointestinal bleeding, peripheral edema, or exacerbation of hypertension—from NSAIDs. The total daily dose of glucosamine sulfate is 1,500 mg in divided doses bid or tid. A trial of at least six weeks seems appropriate to assess whether the patient experiences significant pain relief. Glucosamine also is appropriate to use in conjunction with NSAIDs in patients with incomplete response. A trial of 1,500 mg/d for six weeks also would be appropriate under these circumstances. However, glucosamine cannot be recommended to guard against the onset of OA or as an agent that might prevent the progression of early OA. ❖

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Ginseng to Enhance Sports Performance

By Dónal P. O'Mathúna, PhD

SPORTS SUPPLEMENTS SALES AMOUNTED TO $1.4 BILLION in the United States in 1999, or about 10% of the dietary supplement market.[1] Of all the herbal remedies used by athletes, more clinical research has examined ginseng, consistently the second most popular herbal remedy sold in the United States.[2] Traditional Chinese medicine (TCM) uses ginseng as an adaptogen—a substance that helps the body adapt to stressful situations and promotes general well-being.[3] Ginseng is popularly believed to boost one's energy levels, which makes it attractive to athletes hoping to improve their performances. Unfortunately, the science doesn't live up to the sales, with studies consistently showing that ginseng does not enhance sports performance among athletes.

Herbal Background

Ginseng exemplifies some of the complexities and difficulties surrounding herbal remedies. The term "ginseng" applies to several plant species. The ginseng of TCM is Asian, Chinese, or Korean ginseng (*Panax ginseng*), with American ginseng being the closely related *Panax quinquefolius*. Several other *Panax* species are used in Japanese, Vietnamese, San-chi, and Tien-chan ginseng.[4] Siberian ginseng (*Eleutherococcus senticosus*) is related distantly to the *Panax* species, and Brazilian ginseng is botanically unrelated (*Pfaffia paniculata*).[5]

The active ingredients in Asian and American ginseng are a group of about 30 steroidal glycosides called ginsenosides.[4] However, the ginsenoside levels vary according to species, season harvested, age of the plant, soil, and part of the root used; in 20 American ginseng plants harvested from a 1 square-meter area, the ginsenoside content varied more than twofold.[6] Traditionally, Asian ginseng is harvested after at least five years of growth, at which time the roots typically contain 1-2% ginsenosides.[3] Siberian ginseng contains no ginsenosides, but instead contains other steroidal glycosides called eleutherocides.

Mechanism of Action

Several mechanisms of action have been proposed for ginseng. In TCM, ginseng is believed to restore a balanced flow of *Qi*, or life energy. Animal studies have shown that isolated ginsenosides can stimulate or depress the central nervous system; increase production of corticotrophin and cortisol; stimulate synthesis of DNA, RNA, and protein; and act as immunostimulants or antioxidants.[3] No consensus exists concerning whether any or all of these actions contribute to ginseng's effects on athletes.

Clinical Studies

Asian and Siberian ginseng are most commonly promoted as beneficial for athletes. Asian ginseng has been examined in clinical trials with athletes since the early 1970s. In the early 1980s, Dr. Imre Forgo published five small studies in Germany with elite athletes.[7] Those taking two 100 mg capsules daily of a standardized product, G115® (Ginsana®, Pharmaton), had improved oxygen absorption, reduced blood lactate levels, reduced heart rates, and improved subjective feelings of physical fitness.[8] However, some of these studies did not use control or placebo groups, and used indirect measures of oxygen consumption and submaximal workloads.[9]

Since 1990, several better-designed trials have been published,[10] but nearly all report small numbers and test healthy adults of various fitness levels. Studies using ginseng in combination with other supplements will not be considered here. Two studies of Asian ginseng alone showed some ergogenic effects from ginseng, though neither were clearly beneficial. A randomized, double-blind, crossover study involving 43 female triathletes used 400 mg/d G115.[11] Ginseng provided no exercise advantage during the first 10-week period. During the second 10-week period, those taking ginseng had significantly lower blood lactate during exercise but no performance advantage. The researcher concluded that ginseng may delay end-of-season tiredness, but cautioned that a carryover effect from the first period may have contributed to this finding. This hypothesis was not tested in this study.

In a small study of strength and fitness, 41 students were randomly assigned to four groups.[12] Group 1 took a standardized ginseng extract (150 mg bid) and rode an exercise bicycle for 30 min three times a week. Group 2 exercised the same way and took a placebo. Group 3 took

ginseng without exercising, and Group 4 took a placebo without exercising. After eight weeks, Group 1 had greater leg strength compared to Group 2 ($P < 0.05$), but nonsignificant differences in 10 measures of physiological fitness. Comparing Groups 3 and 4 (neither exercising), those taking ginseng showed significant improvements in maximal oxygen uptake, resting heart rate, and leg strength. The authors concluded there was "no clear synergistic action" between exercise and ginseng.

A number of other well-performed, similarly designed, double-blind studies confirm these conclusions and have found no significant differences between the two groups in maximum heart rate, maximum oxygen consumption, respiratory exchange rate, or total workload.[5,9,13-15] For example, a randomized, double-blind, crossover trial used 28 moderately fit adults taking 200 mg of a 7% ginsenoside standardized extract.[16] Subjects took ginseng or placebo for 21 days and before and afterward performed a graded exercise test on an ergometer. No significant differences were observed for VO_2, exercise time, workload, heart rate, rate of perceived exertion, or blood lactate and hematocrit.

Some suggest ginseng may enhance physical performance via improved concentration, alertness, and arousal. A randomized, double-blind trial of ginseng's psychological effects used 400 mg/d standardized ginseng extract with 112 adults (mean, 51 years).[17] After eight to nine weeks, those taking ginseng had slightly faster reaction times, though statistically significant only for the 10th percentile scores and not for mean scores. Abstract thinking was significantly improved, but not memory, concentration, or well-being. Ginseng has not been beneficial in some psychological studies.[18]

One crossover study examined the ergogenic effect of American ginseng using an extract made for the study.[19] Eight subjects of varying fitness levels were randomly assigned to either 8 mg/kg or 16 mg/kg of ginseng or placebo. After seven days subjects completed a time-to-exhaustion test on a cycle ergometer. The two ginseng groups showed no differences, so their results were combined. Time to exhaustion, oxygen consumption, respiratory exchange rate, and blood levels of lactate, free fatty acids, and glucose showed no significant differences between ginseng and placebo.

The ergogenic effects of Siberian ginseng have been studied in two controlled trials since 1990. The first randomly assigned 20 highly trained distance runners as matched pairs to 3.4 mL of an alcoholic solution of ginseng or placebo.[20] Exercise tests were conducted every two weeks on a treadmill where athletes ran for 10 min at 10 km race-pace and then to exhaustion. No significant differences were found in several respiratory measurements, time to exhaustion, heart rate, or blood lactate levels.

The second Siberian ginseng study used a randomized, double-blind, crossover design with 10 highly trained male cyclists.[21] Subjects took 1,200 mg Siberian ginseng or placebo for seven days prior to conducting a 120 min cycle at 60% VO_{2max} followed by a 10 km time trial. No significant differences were found at any point

Table 1

Studies conducted during the 1990s on the ergogenic effects of ginseng

Study	Study Type	Subjects	Formulation	Duration	Results
Van Schepdael[11]	randomized, double-blind, crossover	43 female triathletes	400 mg/d G115	10 weeks	Reduced blood lactate during second 10-week period
Cherdrungsi[12]	randomized, double-blind, four groups	41 students	150 mg bid standardized extract	8 weeks	"No clear synergistic action" between exercise and ginseng
Engels[9]	randomized, double-blind	19 healthy adult females	200 mg/d G115	8 weeks	No significant ergogenic effects
Engels[5]	randomized, double-blind	36 healthy adult males	200 or 400 mg/d G115	8 weeks	No significant ergogenic effects
Kolokouri[13]	randomized, double-blind	24 healthy adult females	400 mg/d standardized extract	8 weeks	No significant ergogenic effects
Engels[14]	randomized, double-blind	12 aerobically fit young adults	1 g/d ginseng root	60 days	No significant ergogenic effects
Lifton[15]	randomized, double-blind, crossover	11 well-trained amateur cyclists	3 g/d ginseng	13 days	No significant ergogenic effects
Allen[16]	randomized, double-blind, crossover	28 moderately fit adults	200 mg/d 7% ginsenoside standardized extract	21 days	No significant ergogenic effects

between ginseng and placebo in oxygen consumption, respiratory exchange ratio, heart rate, rating of perceived exertion, or plasma lactate and glucose levels.

Adverse Effects

Adverse effects of ginseng were not reported in the clinical trials with athletes, but have been reported occasionally with other users. Adverse effects have not been reported with American ginseng, and very rarely are they reported for Siberian ginseng. However, Asian ginseng has been reported to occasionally cause mastalgia, vaginal bleeding, amenorrhea, tachycardia, edema, hypotension, palpitations, mania, decreased appetite, hyperpyrexia, pruritus, rose spots, headache, vertigo, euphoria, and neonatal death.[22] The incidence of adverse effects increases when use is extended beyond three months, though estimates of the increase are not available. A "ginseng-abuse syndrome" has been proposed for the regular consumption of more than 3 g/d ginseng. The symptoms are hypertension, nervousness, sleeplessness, and diarrhea.[4]

The quality of ginseng products in the United States is of serious concern. One analysis found that only nine of 22 products passed a quality control test, with eight containing greater than allowed pesticide levels.[23] Ginseng is not banned by the International Olympic Committee or the National Collegiate Athletic Association, but an athlete at the 1988 Seoul Olympic Games tested positive for ephedrine, which is banned. The ephedrine was traced to a ginseng product.[24]

Drug Interactions

Very little evidence exists here, although theoretically ginseng's many constituents could interact with several drugs. All ginseng species potentiate caffeine's stimulant effects, suggesting caution when taken with tea, coffee, and herbs like guarana or mate. Reports exist of Asian ginseng interfering with warfarin and other blood-thinning agents, though inconsistently. Theoretically, all ginseng species could interfere with antidiabetic agents, antipsychotic drugs, steroids, and with drugs metabolized by the cytochrome P450 enzyme system.[23]

Formulation

Ginseng plant material is processed in several ways, leading to further variability in ginsenoside content. The roots are most commonly bleached and dried, producing "white ginseng."[3] If the roots are steam-cured prior to drying, this gives "red ginseng." Teas, extracts, and tinctures (alcohol-based extracts) are available, leading to even greater variability.

In TCM, 3-9 g/d of powdered ginseng root is taken, usually combined with other herbs.[3] Standardized preparations typically contain 4% ginsenosides, with 200 mg/d ginsenosides recommended. Many clinical trials used a standardized preparation called G115.

Conclusion

Although animal studies consistently have found exercise benefits from ginseng and ginsenosides, these studies have tended to use much higher doses than those given to humans (up to 100 times higher). A number of early human studies found significant ergogenic effects, which gave ginseng use much credibility among athletes. The Ginsana web site continues to cite these studies from the 1980s, but fails to mention that several, better-designed studies have not reproduced these results.[8]

The results of ginseng research are complicated by varying doses, plant species, and product formulations. Studies have been conducted for different lengths of time and used different outcome measures. However, lack of efficacy has emerged as the most consistent result. Although the research protocols may vary from how athletes use ginseng, the evidence fails to demonstrate that ginseng has any direct impact on athletic performance.

Recommendation

Ginseng is widely used by the general population and among athletes. Although adverse effects are relatively infrequent, the lack of direct ergogenic effect should caution athletes against taking ginseng. Some hold that ginseng offers athletes psychological benefits that enhance performance. However, these effects have not been examined in competitive situations. Athletes should beware that contaminants are found regularly in ginseng products, some of which are substances banned by sports organizations. Given the lack of efficacy, any risk of adverse effects, and the small chance of inadvertently consuming a banned substance, athletes should be discouraged from taking ginseng. Research does not support its use as an ergogenic aid. ❖

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Acupuncture for the Treatment of Infertility

By Judith Balk, MD, FACOG

A COMMON CONDITION SEEN IN MEDICAL PRACTICE, infertility is described in Western medicine as the inability of couples of reproductive age to establish a pregnancy by having sexual intercourse within a certain period of time, usually one year.[1] Causes include anovulation, pelvic factors such as adhesions and tubal occlusion, cervical factors, and male factors such as oligozoospermia, low sperm motility, or low volume of semen. In Western medicine, treatment is aimed at correcting the etiological factor after ruling out other causes of infertility.

Etiology in Traditional Chinese Medicine

According to traditional Chinese medicine (TCM), the etiology of infertility also may be multifactorial, and may include constitutional weakness, overwork, excessive physical work, excessive sexual activity at an early age, invasion of cold, and diet.[2] TCM treatment attempts to correct the underlying problem through use of herbal

preparations and acupuncture. Prescriptions date back hundreds of years, and as early as 259 AD, acupuncture formulae were given for infertility. Prescriptions varied based on the presence or absence of clinical factors such as abdominal pain, white vaginal discharge, and stasis of blood.[2]

In TCM, male infertility is thought to be caused by kidney deficiency. Treatment is aimed at promoting the circulation of *Qi* and blood and at regulating yin and yang. Additional aims are to promote the generation of vital essence and to enrich the source of vital energy and the essence of kidney.[3]

Mechanism of Action

The mechanisms of action by which acupuncture may treat infertility have not been elucidated. One possible mechanism is via hormonal regulation, with acupuncture regulating a dysfunctional hypothalamic-pituitary axis. Another mechanism might be improvement in uterine blood flow, which increases the receptivity of the endometrium to a fertilized egg.

Research Base

A MEDLINE search of the terms acupuncture and acupuncture therapy plus infertility revealed 10 journal articles since 1966. Seven of these are in English. Using the Cochrane Controlled Trials Register, two new clinical trials were obtained using the same search terms. Although five trials had control groups, only two of seven trials were randomized. Other studies are case series or a case report. Unfortunately, the lack of randomization limits the utility of the rest of these studies. One controlled trial included both animals and humans.

Animal Studies

One animal study was performed in China.[4] The article was difficult to read and interpret, in part because of a language barrier and in part because of the study's complexity. Briefly, half of the rats underwent ovariectomy; then, half of the ovariectomized rats and half of the intact rats received electroacupuncture. At the completion of the study, the animals were sacrificed and studied.

The authors found that acupuncture in the ovariectomized rats induced maturation of the vaginal cells and increased blood concentrations of estradiol. Acupuncture also enlarged the adrenals and increased concentrations of corticosterone and beta-endorphin and decreased gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH). The authors conclude that the effects of acupuncture may be to "promote the function of hypothalamic-pituitary-adrenal axis, increasing the synthesis and secretion of adrenal steroid hormones, the androgen of which then be (SIC) transformed into estrogen in other tissues and thereby reset the negative feedback of estrogen to hypothalamic-pituitary-ovarian axis." If correct, this hypothesis would result in an estrogenic stimulus.

Human Female Studies—Treatment

Infertile patients may seek assisted reproductive techniques such as in vitro fertilization (IVF). Successful IVF depends on adequate endometrial receptivity. Acupuncture has been demonstrated to improve uterine blood flow impedance, which is a measurement of blood flow to the uterus. It has been considered valuable in assessing endometrial receptivity.[5] Ten subjects with a high pulsatility index, a measurement made using Doppler transvaginal ultrasound, were treated with twice weekly acupuncture for the month prior to embryo transfer. A high pulsatility index is evidence of decreased uterine artery blood flow. Pulsatility index decreased both at the time of the embryo transfer and again at follow-up approximately two weeks later. The authors suggest that the effects arise from a central inhibition of the sympathetic activity.

Acupuncture also has been studied as analgesia during infertility treatment. A randomized controlled trial compared acupuncture to alfentanil as anesthesia for oocyte aspiration during IVF.[6] One hundred fifty women participated in this study. The acupuncture group experienced discomfort for a longer period of time during oocyte aspiration, but no differences between the groups were noted by visual analog scale, adequacy of anesthesia during aspiration, abdominal pain suffered, or degree of nausea. Surprisingly, the acupuncture group had a statistically significantly higher implantation rate, pregnancy rate, and take home baby rate per embryo transfer. Compared with the alfentanil group, the electroacupuncture group's implantation rate was 27.2% vs. 16.3%; pregnancy rate was 45.9% vs. 28.3%; and take home baby rate was 41% vs. 19.4% per embryo transfer. The same authors are conducting a larger study to corroborate these findings.

A large fibroid may cause infertility. One case report presented a patient with a 13 x 8 x 10 cm fibroid uterus who had secondary infertility, unresponsive to "repeated" cycles of IVF.[7] The exact number of IVF cycles was not reported. This patient underwent acupuncture treatment and her uterus decreased to 7 x 8 x 8 cm, after which she had successful IVF and delivered healthy twins.

The studies cited above all used body points, but auricular (or ear) acupuncture also has been used to treat female infertility.[8] Forty-five infertile women with either

oligomenorrhea or luteal insufficiency were treated with auricular acupuncture. Results of treatment were then compared with matched subjects who were treated with hormones. Pregnancy rate was similar for both groups, whereas side effects were observed only in the hormone group. However, the groups were not equal even though they were matched on several criteria. The authors conclude that auricular acupuncture seems to offer a valuable alternative therapy for female infertility from hormone disorders. However, lack of randomization and differences between the groups limit the ability to make this conclusion.

Human Female Studies—Hormone Levels

Chinese investigators studied 10 anovulatory women and five women with normal menstrual cycles.[4] Subjects were treated with electroacupuncture for 30 min/d for three days per month for 13 cycles. Changes in blood hormone concentration were measured. Beta-endorphin, LH, and follicle-stimulating (FSH) normalized in those who ovulated but did not change in those who did not ovulate. However, the determination of ovulation was not described, and other important methodological details are missing.

Another Chinese study was equally difficult to interpret.[9] Thirty-four subjects with amenorrhea and dysfunctional uterine bleeding received acupuncture three times per week for three months. The terms that the authors use are unclear. Criteria for the efficacy of therapy for inducing ovulation were defined as markedly effective, effective, or ineffective, based on ultrasound, basal body temperature, and presence or absence of menstruation. Thirty-five percent, 48%, and 18% were markedly effective, effective, and ineffective, respectively. An endocrine profile was performed in 20 subjects before and after treatment. FSH, LH, and estradiol normalized compared to pre-acupuncture values. However, the time during the menstrual cycle at which the blood was drawn was not stated; different timing could greatly skew these results.

Human Male Studies

Four studies report on acupuncture as treatment for male infertility. One report is a prospective, non-randomized, controlled trial.[10] Men were "subfertile," defined by lack of conception and abnormal semen analysis. Criteria for defining abnormal semen analysis are not stated. Sixteen subfertile men were treated with acupuncture twice per week for one month and were compared with 16 subfertile men who received no acupuncture. Blinded observers read the semen analyses. At baseline, both groups had similar results. No changes occurred in the untreated group at follow-up, whereas the treated group improved in three aspects of the semen analysis: percentage of sperm viability, total number of motile sperm, and total functional sperm fraction. Four spontaneous pregnancies occurred following the acupuncture treatment, but how soon after the treatment the pregnancies occurred is not stated.

A larger Chinese study was a randomized, controlled trial of 297 men with infertility.[3] In this study, patients were randomized to receive various combinations of acupuncture, point-injection of essence of pilose antler, and oral administration of Chinese materia medica, which is an herbal prescription consisting of eight different compounds; thus, five different groups of subjects were formed. The materia medica preparation was individualized based on symptoms. All patients received acupuncture as part of the treatment. Baseline and follow-up semen analyses were performed on all subjects.

Of the 297 cases, roughly half were "cured," meaning pregnancy occurred. Approximately one quarter normalized their semen analysis, and the rest continued to have abnormal semen analyses. Of the five groups, treatment with all three modalities yielded the best results and oral drugs plus injection yielded the worst results. Those men with aspermia or very low sperm count (≤ 1 million) had fewer cured cases than those with higher sperm counts. Also, the therapeutic effects were better in younger compared to older patients. Statistical analysis, adequate definitions of therapeutic effect, and method of randomization are not presented in this article. Obviously, the modality of injecting drug into acupuncture points is not commonly used in Western countries.

Lastly, a German abstract describes an attempt to treat subfertility in 28 males, noting that the experiences in veterinary medicine encourage them to attempt this type of therapy.[11] Total count, concentration, and motility all improved following acupuncture for three weeks. Again, abstracts do not give sufficient information to make firm conclusions.

Conclusion

A small number of studies have been conducted to investigate the effect of acupuncture on both male and female infertility. Lack of rigorous design, inadequate definitions, and language barriers all make the present data unconvincing.

Recommendation

Although many of the above studies indicate the potential effectiveness of acupuncture on infertility, each study is limited by lack of rigorous study methods. In the absence of rigorous methodology, the data are not

persuasive either in favor of or against acupuncture in the treatment of infertility. More research is absolutely necessary to make a firm conclusion about effectiveness. ❖

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News Briefs

Safety Concerns: Aristolochic Acid

In April 2001, the Food and Drug Administration (FDA) issued an alert to health care professionals regarding safety information about botanical products containing aristolochic acid, an ingredient in dietary supplements and other "traditional medicines." This letter follows an earlier letter from May 2000 that warned of nephrotoxicity and carcinogenicity of botanicals containing aristolochic acid. Since the earlier letter, and since publication of a warning about aristolochic acid in this publication (see *Alternative Medicine Alert*, August 2000, p. 95), additional information has surfaced regarding adverse effects from this harmful ingredient. Renal disease or malignancies associated with use of botanical preparations should be reported as soon as possible to the FDA's MedWatch program by phone (800-332-1088) or the Internet (http://www.fda.gov/medwatch). ▼

FDA Warns Food Manufacturers

The FDA in January 2001 sent warning letters to conventional food manufacturers whose products contain botanical ingredients or extracts, reminding companies that these additives must be proven safe before they can be added to food products. Since the initial letters in February, the number of food products containing herbal additives has grown, prompting the FDA to begin sending warning letters to specific manufacturers demanding that they prove the safety of herbal additives. ❖

CME Questions

1. **Clinical trials of glucosamine have found it effective for which of the following osteoarthritis symptoms?**
   a. Pain relief
   b. Stiffness
   c. Functional disability
   d. All of the above
2. **Most clinical research on ginseng for athletic performance has been conducted on:**
   a. American ginseng.
   b. Asian ginseng.
   c. Siberian ginseng.
   d. Brazilian ginseng.
3. **The use of ginseng by athletes is banned by:**
   a. the International Olympic Committee (IOC).
   b. the National Collegiate Athletic Association (NCAA).
   c. both the IOC and the NCAA.
   d. neither the IOC nor the NCAA.
4. **The research base is adequate to make a firm conclusion in favor of acupuncture as effective treatment for infertility.**
   a. True
   b. False
5. **Which of the following approaches has been studied as a treatment for infertility in men?**
   a. Acupuncture
   b. Point injection
   c. Oral administration of herbs
   d. Massage therapy

With Comments from John La Puma, MD, FACP

Ipriflavone for Osteoporosis

Source: Alexandersen P, et al. Ipriflavone in the treatment of postmenopausal osteoporosis: A randomized controlled trial. *JAMA* 2001;285:1482-1488.

DATA ON THE EFFICACY AND SAFETY of ipriflavone for prevention of postmenopausal bone loss are conflicting. To investigate the effect of oral ipriflavone on prevention of postmenopausal bone loss and to assess the safety profile of long-term treatment with ipriflavone in postmenopausal osteoporotic women, we conducted a prospective, randomized, double-blind, placebo-controlled, four-year study in four centers in Belgium, Denmark, and Italy from August 1994 to July 1998.

We enrolled 474 postmenopausal white women, ages 45 to 75 years, with bone mineral densities (BMDs) of less than 0.86 g/cm^2. Patients were randomly assigned to receive 200 mg ipriflavone tid (n = 234) or placebo (n = 240); all received 500 mg/d of calcium. Efficacy measures included spine, hip, and forearm BMD and biochemical markers of bone resorption (urinary hydroxyproline corrected for creatinine, and urinary CrossLaps [Osteometer Biotech, Herlev, Denmark] corrected for creatinine), assessed every six months. Laboratory safety measures and adverse events were recorded every three months.

Based on intent-to-treat analysis, after 36 months of treatment, the annual percentage change from baseline in BMD of the lumbar spine for ipriflavone vs. placebo (0.1% [95% confidence interval {CI} -7.9% to 8.1%] vs. 0.8% [95% CI -9.1% to 10.7%]; P = 0.14), or in any of the other sites measured, did not differ significantly between groups. The response in biochemical markers also was similar between groups (e.g., for hydroxyproline corrected for creatinine, 20.13 mg/g [95% CI 18.85-21.41 mg/g] vs. 20.67 mg/g [95% CI 19.41-21.92 mg/g]; P = 0.96); urinary CrossLaps corrected for creatinine, 268 mg/mol (95% CI 249-288 mg/mol) vs. 268 mg/mol (95% CI 254-282 mg/mol); P = 0.81. The number of women with new vertebral fractures was identical or nearly so in the two groups at all time points. Lymphocyte concentrations decreased significantly (500/microliters [0.5 x 10^9/L]) in women treated with ipriflavone. Thirty-one women (13.2%) in the ipriflavone group developed subclinical lymphocytopenia; 29 developed it during ipriflavone treatment. Of these, 15 (52%) of 29 had recovered spontaneously by one year and 22 (81%) of 29 by two years.

Our data indicate that ipriflavone does not prevent bone loss or affect biochemical markers of bone metabolism. Additionally, ipriflavone induces lymphocytopenia in a significant number of women.

COMMENT

Ipriflavone, a derivative of the naturally occurring class of isoflavones, found mainly in soy, is marketed and approved in Europe to prevent bone loss. The Ipriflavone Multicentre European Fracture Study (IMEFS) is a large study of nonobese postmenopausal women with low bone density. The design is a three-year, randomized, double-blind, placebo-controlled, parallel group study. Its primary purpose is to evaluate the efficacy of ipriflavone in preventing vertebral non-traumatic fractures.

Although only 292 of 492 individuals completed the study, the results were unfavorable. Postmenopausal women with established osteoporosis but without vertebral fractures did not have better bone density, though this claim is not usually made for ipriflavone. Balk notes, "The majority of the (previous ipriflavone) studies found that bone mass was not increased in the ipriflavone group, but that it was decreased in the control group, with significant between-group differences." (See *Alternative Medicine Alert*, December 2000, pp. 133-137.) The IMEFS did not have sufficient power to detect an effect of ipriflavone on fracture incidence. Studies of bisphosphonates or raloxifene typically attempt to enroll hundreds or even thousands of patients to detect such an incidence.

Previously noted lymphocytopenia was indicated here as well. The women remained immunologically healthy, and it is unknown whether the lymphocyte subpopulations CD4 and CD8 were affected equally. Still, one of eight study women was determined to be lymphocytopenic—certainly a finding that needs verification.

Does this mean ipriflavone doesn't work in this population? Not yet, though this is the best evidence we have. The dosage may have been suboptimal, the power inadequate to detect statistically significant differences, or the study population too osteoporotic. Ipriflavone appears not to increase bone density in nonobese, postmenopausal osteoporotic women, but whether it improves fracture incidence is still uncertain.

Recommendation

These data do not support the use of ipriflavone to prevent bone density loss, but they are not the final word. Women with hematological and immune disorders and hormone-dependent cancers, and women who are breast feeding or pregnant should avoid ipriflavone, as its metabolites may have estrogenic effects. ❖

In Future Issues:

Yarrow as a Poultice
Gymnema sylvestre for Diabetes
Deer Antler Velvet for Impotence

Supplement to *Alternative Medicine Alert*
July 2001

ALTERNATIVE MEDICINE ALERT™
A Clinician's Evidence-Based Guide to Alternative Therapies

Selenium

THE ASSOCIATION BETWEEN SELENIUM, AN ESSENTIAL TRACE MINERAL, AND CANCER GAINED prominence as a result of epidemiologic studies from the 1960s and 1970s that showed an inverse relationship between selenium intake and the incidence of leukemia and colon, rectal, pancreatic, breast, ovarian, prostate, bladder, lung, and skin cancers, as well as overall cancer mortality.

A retrospective study in the 1980s supported these epidemiologic findings: Subjects with the lowest serum selenium concentrations had twice the risk of several cancers, including breast cancer, as did those with the highest concentrations.[1] Many recent case-control and prospective studies boast positive results,[2-3] but others have not or have been confounded by the presence of multiple antioxidant agents in the intervention design.[4-5]

Although questions remain, the clinical evidence does point to an association between selenium levels and cancer risk. Currently, an eight-year, prospective study of 12,000 men and women is under way in France.[6] This study may help clarify the effect of selenium supplementation on the incidence of many chronic diseases.

Dietary Reference Intakes (DRI)

15 mcg/d for children 0-6 mo
20 mcg/d for children 7 mo-3 y
30 mcg/d for children 4-8 y
40 mcg/d for children 9-13 y
55 mcg/d for children 14-18 y
55 mcg/d for adults 19 y and older

Food Sources

- Dietary sources of selenium include Brazil nuts, tuna canned in oil, beef liver, cod, enriched grain products, turkey, chicken, eggs, cheese, walnuts, broccoli, mushrooms, and garlic.
- The selenium content of plant foods varies depending upon the presence of selenium in the soil where the plants are grown.Variability exists within the United States.

Mechanism of Action

- Selenium is an antioxidant that regulates the activity of glutathione peroxidase enzymes.

Clinical Uses

- To prevent osteoarthritis, rheumatoid arthritis, and Kashin-Bek disease, a form of deforming arthritis.
- To prevent Osgood-Schlatter disease and Keshan disease, an endemic cardiomyopathy.
- To prevent cardiovascular disease.
- To treat asthma.
- To prevent skin, liver, hepatic, prostate, and colon cancer.
- To prevent macular degeneration and cataracts.
- To treat selenium deficiency commonly associated with HIV/AIDS.
- To improve immune function.

- To prevent liver necrosis.
- To treat abnormal testosterone metabolism.

Formulations

- It has been argued that organic selenium (selenomethionine) is absorbed better than inorganic selenium (selenite); however, there is no evidence to support this claim.

Adverse Effects/Toxicity

- Selenium can cause symptoms of acute toxicity including nausea, vomiting, nail changes, fatigue, and irritability.
- Chronic toxicity resembles arsenic toxicity. Symptoms include hair loss, white horizontal streaking on fingernails, paronychia, fatigue, irritability, hyperreflexia, nausea, vomiting, garlic odor on breath, and metallic taste. Muscle tenderness, tremor, lightheadedness, and facial flushing also may be observed.
- Selenium toxicity has been reported with mean doses greater than 800 mcg/d, with a 95% confidence limit of 600 mcg/d.
- Blood selenium levels can be used to assess the degree of toxicity: levels below 1,000 mcg/L usually are not associated with serious damage; levels above 2,000 mcg/L usually are predictive of serious damage.
- Selenium toxicity can elevate the ST segment and cause T-wave changes characteristic of myocardial infarction.
- Selenium toxicity can elevate serum creatinine kinase levels.

Interactions/Nutrient Depletion

- Selenium levels can be decreased by smoking, alcohol, and oral contraceptives.
- Vitamin E appears to decrease the oxidative damage seen in selenium deficiency; concomitant use of selenium and vitamin E may be beneficial in selenium-deficient individuals. Concomitant use also appears to have synergistic effects on the treatment of heart disease, ischemia, and cancer.
- Use of inorganic sodium selenite or selenate has been noted to interact with ascorbic acid, leading to decreased absorption of selenium.
- Concomitant use of vitamin C may produce synergistic effects; however, large doses of vitamin C may decrease selenium absorption.
- Selenium is essential for the synthesis of active thyroid hormone; therefore, selenium deficiency may affect thyroid function and may worsen the effects of iodine deficiency on thyroid function.
- In comparison to cisplatin treatment alone, concomitant use of selenium can increase the cytotoxic effects of cisplatin in the presence of chelate ethylenediaminetetraacetic acid.
- When testing blood for selenium and other trace elements, avoid powdered gloves to reduce the potential of sample contamination.
- Individuals on total parenteral nutrition or with a digestive disorder, such as Crohn's disease, that can impair selenium absorption may require selenium supplementation.

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