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Glucosamine Sulfate for the Treatment of Osteoarthritis

By David Schiedermayer, MD, FACP

Archeological studies of ancient humans reveal they had osteoarthritis (OA) of the lateral compartment of the knee (they were, like cowboys, bowlegged). Modern humans have OA primarily in the medial compartment (they are obese and have valgus deformity, knock-kneed).

This clinical fact, which I observe daily in my clinic, has always intrigued me as a teacher. We don't know what causes OA, exactly, but we do know that it is associated with obesity, a profound problem for modern Americans. This should be the starting point for the discussion of any "pills," "natural" or "synthetic," which claim to have any effect on this disease. I have had several patients avoid or postpone hip replacements "simply" by losing 20-30 pounds.

Nonetheless, the prospect of a nutritional remedy for the treatment or prevention of OA is compelling, particularly because no specific medications currently halt disease progression. The problem is enormous, because more than four out of five persons older than the age of 65 show some clinical or radiological evidence of the disease. Glucosamine sulfate (GS) has been touted as a possible cure in *The Arthritis Cure*.[1] Is there any merit to such a claim?

Pathogenesis and Current Treatment

OA, or degenerative joint disease (DJD), is a slowly progressive disease involving ongoing breakdown of articular cartilage and changes in the subchondral bone. The precise biochemical cause is unknown, but the process is characterized by a predominance of degradation (over repair) of cartilage proteoglycans and of subchondral bone. Over time, the continued catabolism of proteoglycans results in abrasion of the articular cartilage and the formation of new bone in the joint. This leads to functional deterioration, which results in stiffness, joint swelling, deformity, and crepitus. Synovitis can occur from the release of various inflammatory mediators, including collagenase, gelatinase, and activation of chondrocytes. Additional predisposing factors include aging, heredity, mechanical stress, obesity, crystalline deposits, previous inflamma-

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tory disease, and metabolic abnormalities. Given the involvement of cartilage in the process, "chondroprotective" agents are desirable.[2]

The current recommended treatment for OA is weight loss, physical therapy, and the use of pain relievers including acetaminophen and nonsteroidal anti-inflammatories (NSAIDS). NSAIDS have been reported to have positive and negative effects on cartilage metabolism. They prevent the activation of tissue-destroying enzymes by inhibiting cyclooxygenase, but they have been shown (in vitro) to reduce glycosaminoglycan synthesis in canine cartilage[3] and indomethacin has been shown to speed the progression of OA in humans.[4] NSAIDS and acetaminophen do not reverse OA.[5]

Background

In vitro studies dating back to the 1950s have shown the addition of exogenous GS to cartilage-derived fibroblasts enhances secretion of mucopolysaccharides and collagen. The first studies used injectable GS preparations, but studies in humans in the early 1980s used the oral formulation of GS 500 mg and demonstrated mild effectiveness and virtually no toxicity.[6]

Mechanism of Action

GS is the salt of D-glucosamine, an amino sugar, with sulfuric acid. In solution, GS dissociates into the D-glucosamine ion and the sulfate ion. Most authors think that the glucosamine ion is the active principal, but at least some evidence suggests that a component of the GS activity is related to sulfur residues, because sulfur is an essential nutrient for the stabilization of connective tissue matrix.[7]

Controversy exists as to whether oral glucosamine avidly and preferentially seeks joint cartilage: proponents argue that the studies show that it is concentrated more in articular cartilage than any other tissue. This should be a provable hypothesis, using radiolabeling techniques, and it seems an important area for future research.

Biochemistry

Glucosamine can pass through biological membranes easily because it has a molecular weight of only 179 daltons. It is found in vivo as glucosamine 6-phosphate and is required for the biosynthesis of glycolipids, glycoproteins, mucopolysaccharides, hyaluronic acid, and proteoglycans.

Glucosamine's primary role is as a substrate for the glycosaminoglycans and the hyaluronic acid backbone used in the formation of the proteoglycans found in the structural matrix of joints.[7] When taken by mouth, as would be the case with any simple sugar, a substantial portion is metabolized into H_2O, CO_2, and urea.

Clinical Studies and Use

In short-term controlled trials, glucosamine has been effective in relieving pain and increasing range of motion in OA patients.[6] One four-week, double-blind trial in 252 patients with OA of the knee found oral GS 500 mg tid was more effective than placebo.[8] In a four-week, double-blind trial of 200 patients, glucosamine sulfate was as effective as ibuprofen 400 tid from the second week onward.[9] In a double-blind, eight-week study of 40 patients with OA, GS was as effective as ibuprofen 400 tid in relieving pain after two weeks, and by the end of the trial was more effective.[10]

Most of the current data are derived from European and Asian literature. The studies published to date have been done in small numbers of patients; adequate long-term trials examining the safety, efficacy, and optimal dosage requirements of glucosamine are lacking.[2] However, six double-blind investigations in five countries all have documented statistically significant benefits, without side effects.

NSAIDS studies, in comparison, demonstrate significant side effect rates of 10-20%. A systematic review of 43 randomized controlled trials of NSAIDS and analgesic therapy in OA revealed that selection of the best NSAID for a particular patient is an art as well as a science. Remarkable variations in individual patient re-

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sponses, side effects, and preferences for individual NSAIDS existed. Four of the randomized clinical trials evaluated the efficacy of simple analgesia, but did not include any analysis of GS studies.[11]

Patient education interventions are also important in OA management. A meta-analysis of 19 patient education trials comprised of 32 treatment arms and 28 NSAID trials comprised of 46 treatment arms revealed that patient education interventions provide additional benefits that are 20-30% as great as the effects of NSAID treatment for pain relief and 40% as great for improvement in functional ability.[12]

Adverse Effects

In vitro studies have consistently demonstrated low toxicity; no LD50 has been established, since even at the very high levels of 5000 mg/kg, there is no mortality in mice and rats.

In human studies, less than a 4% incidence of GI effects, such as discomfort and nausea, have been reported, and severe side effects, such as edema and tachycardia, were reported in 0.08% of subjects.[13] GS should not be consumed during pregnancy or childbearing years, and GS should not be consumed by young children until safety studies are performed. Diabetics should be cautious taking glucosamine, since it is an amino sugar, and they should check their glucose levels frequently (although documented hyperglycemia has not been a problem to date). Patients should not give up on proven pain management techniques, such as joint protection, exercise, and weight reduction.[14]

As in any therapeutic intervention, misdiagnosis is a potential problem. GS does not treat neuropathic pain, stress fractures, inflammatory arthritis, or other conditions. One must be sure that OA is the cause of pain.

Drug Interactions

No known drug-drug interactions exist, although if patients take preparations also containing chondroitin sulfate, a long chain of amino sugars which is similar in structure to heparin sulfate, possible additive anticoagulative effects may occur.

Formulation/Dosage

The source of GS is the chitin of crab shells. It is relatively inexpensive, depending on the formulation chosen. (*See Table.*) Glucosamine derivatives are available in pharmacies and health food stores as the sulfate, hydrochloride, n-acetyl, or chlorohydrate salt and as the dextrorotatory isomer. GS is sometimes combined with chondroitin sulfate, a glycosaminoglycan that has been reported to maintain viscosity in joints, stimulate cartilage repair mechanisms, and inhibit enzymes that break down cartilage.[15] Chondroitin sulfate is derived from bovine trachea. Chondroitin sulfate, unlike GS, is poorly absorbed from the GI tract. The usual dose, and the one most studied, is glucosamine sulfate 500 mg po tid.

Conclusion

GS is a safe nutritional measure that supports proteoglycan synthesis, and it may offer a practical means of treating, preventing or postponing the onset of OA in older people.[6] It is well absorbed and has a striking lack of side effects, but it also shows no evidence of being a

Glucosamine Popular Remedy for Bodybuilders, Elderly Patients

Although most media coverage and clinical studies of glucosamine involved older patients, an article in the October 1998 issue of *Muscle & Fitness* includes glucosamine as one of several nutrients that can help bodybuilders maintain strong and healthy joints. The article notes that fitness enthusiasts take numerous supplements to improve muscle tone and size and may fail to consider the importance of maintaining the integrity of the joints. Overtraining or improper high-impact training can cause "wear-and-tear" degeneration, and glucosamine may help reduce symptoms. The article recommends taking 1000 mg per day.

Prevention categorized the commercial combination of glucosamine and chondroitin as being "worth a look" in the April 1998 article, "Consumer's Guide to Supplements." The author says preliminary studies have shown this combination reduces pain and slows cartilage loss in osteoarthritis. Readers are told to take the combination for eight weeks and to discontinue taking the supplements at that time if no improvement is seen.

The May/June 1998 issue of *Natural Health* lists glucosamine as one of 10 supplements that can help prevent, delay, stop, or reverse many of the less-pleasant effects of aging. The author says about 20 studies show that glucosamine reduces pain and swelling and can help rebuild lost cartilage, with no side effects, and recommended taking 1500 mg per day.

Not all popular magazines have endorsed glucosamine as a viable treatment. The April 1997 *Tufts University Health & Nutrition Letter* cautions readers that since glucosamine is a dietary supplement and, therefore, not subject to federal regulation, consumers have no assurance that the package claims are accurate. ■

Table

Product Name	Amount of Glucosamine Contained in Each Dose	Dosage Form	Bottle Size (n)	Price Per Bottle* ($)	Manufacturer
Enhanced Glucosamine Sulfate	D-glucosamine sulfate 375 mg	capsule	60, 90	$19.99	General Nutrition Corp.
Glucosamine Complex	glucosamine HCl 250 mg and N-acetylglucosamine sulfate 250 mg	capsule	90	28.95	Vitamin Research Products
Glucosamine Mega 1000	glucosamine HCl 1000 mg	tablet	100	22.49	Jarrow Formulas
Glucosamine Sulfate	glucosamine sulfate 750 mg	capsule	60, 120	44.96	TwinLab
Glucosamine Sulfate	glucosamine sulfate 500 mg	capsule	60	13.99	Great Earth
Glucosamine Sulfate 500	glucosamine sulfate 500 mg	capsule	100, 200	27.95	Jarrow Formulas
Glucosamine Sulfate 500	glucosamine sulfate 500 mg	capsule	60, 120	15.95	The Vitamin Shoppe
Joint Factors	glucosamine sulfate 375 mg	capsule	60, 120	19.96	TwinLab
Nutri-Joint	glucosamine HCl 300 mg and N-acetylglucosamine sulfate 100 mg	capsule	90	38.95	Vitamin Research Products
Tyler Glucosamine Sulfate	glucosamine sulfate 500 mg	capsule	60, 120	38.00	Tyler Encapsulations
Ultra Maximum Strength Glucosamine Sulfate	glucosamine sulfate 600 mg	tablet	60	24.95	Nature's Plus

*Prices vary, depending on bottle size
Adapted from: C da Camara C, Dowless GV. Glucosamine sulfate for osteoarthritis. *Ann Pharmacother* 1998;32:580-587.

"cure" for arthritis. About cure, *The Berkeley Wellness Letter* writes "Unlike bone, cartilage which has been injured has difficulty repairing itself. It is one of the most complex tissues in the body, and nobody knows how to restore it to its original shape. . .It is much too early to recommend GS and chondroitin sulfate as treatments, let alone call them a cure."[16]

Recommendation

Physicians should encourage weight loss, physical therapy, and regular exercise as the primary treatments for OA. For patients seeking pain relief, an 8-12 week trial of GS, 500 mg tid, appears to be much safer and at least as effective as ibuprofen 400 mg tid for many patients with mild-to-moderate OA of the weight bearing joints. Patients should not discontinue their weight loss and exercise programs if they choose to add glucosamine; whether they continue taking an NSAID or acetaminophen while on GS is an individual decision that a patient should make in consultation with his or her physician. ❖

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Gugulipid for the Treatment of Hypercholesterolemia

By Philippe Szapary, MD and Michael Cirigliano, MD

Hypercholesterolemia affects millions of Americans. According to the National Cholesterol Education Program, approximately 40% of Americans need some form of treatment for hypercholesterolemia.[1]

Results from several randomized clinical trials estimate that a 10% reduction in cholesterol level is associated with a 25% reduction in coronary events among patients treated for more than five years.[1] While diet should continue to be the mainstay of therapy, cholesterol-lowering drugs are widely prescribed, with HMG-CoA reductase inhibitors (statins) being the most popular. Statins are expensive and have side effects, prompting many patients to look to alternative therapies.

History

Gugulipid is an extract of the resin from the mukul myrrh tree (*Commiphora mukul*). This thorny tree has little foliage and is indigenous to Western India. Upon injury, this 4 ft. tree exudes a resin called gum guggul, or guggulu, the medicinal uses of which date back to 600 BC. More than 2000 years ago, Ayurvedic texts described atherosclerosis as a stepwise process starting with overeating (medoroga) and lack of exercise, eventually leading to "coating and obstruction of channels."[2] It was for this process that gum guggul was thought most useful. However, it was not until 1966 that the hypolipidemic properties of gugulipid were scientifically tested.

Indian clinical trials performed in the 1970s and 1980s gained the Prime Minister of India's attention in 1987.[2] While its use has not caught on in the United States, gugulipid is now widely used in India for the treatment of hypercholesterolemia.

Pharmacology

The soluble portion of gum guggul is called gugulipid and is extracted using ethyl acetate. The most active ingredients of gugulipid are the ketones E- and Z-guggulsterones.[3] While commercial gugulipid in India is standardized to contain a minimum of 50 mg of guggulsterones per gram of gugulipid, products available in the United States vary in their guggulsterone concentration.

Mechanism of Action

Unlike other lipid-lowering agents, gugulipid appears to have multiple modes of action, though none are particularly well understood. Animal models indicate that gugulipid works by inhibiting lipogenic enzymes and HMG-CoA reductase in the liver.[4] It is also thought to stimulate lipolytic enzymes, enhance fecal excretion of sterols, and act as a bile acid sequestrant.[4] Gugulipid has been shown to stimulate thyroid function in rats.[5]

Clinical Trials

Several studies have shown the efficacy of various fractions of the gum guggul in varied dosages in reducing serum lipids. There are four published human clinical trials evaluating the hypolipidemic effect of standardized gugulipid, all performed and published in India between 1985 and 1994.[6-9] Two of the four studies were placebo-controlled, and only one study directly compared gugulipid to another agent (clofibrate).

The largest trial was a two-phase multicenter study that included 205 patients.[7] In the first phase of this study, patients were placed on a low-fat diet for six weeks before being treated with gugulipid 500 mg tid for 12 weeks and then being switched to a matching placebo for an additional eight weeks. At study entry, this cohort had on average a total cholesterol (TC) of 301 mg/dL and a triglyceride level (TG) of 231 mg/dL. While this was mainly a primary prevention trial, an unspecified number of patients with stable CAD were also included. In the first phase of the study, it was noted that gugulipid significantly decreased TC by 22% and TG by 25% compared to placebo. In the second phase of this same study, 233 patients with a mean TC of 258 mg/dL and mean TG of 282 mg/dL took part in a double-blind, crossover trial with gugulipid and clofibrate.

When informally pooled, the four studies reveal that on average, 70% of patients enrolled lowered both their TC and TG in response to gugulipid. Responders were identified as patients who dropped their TC and TG by more than two standard deviations below the intra-individual week-to-week variation in lipids seen during these trials. These results compare favorably to other hypolipidemic drugs used today in the United States.

These studies have notable weaknesses. Only two of the four measured HDL, and, thus, LDL could not be calculated. The longest follow-up was six months, and data are lacking on cardiovascular events or mortality and on continued effectiveness of gugulipid on serum lipid concentrations.

Other studies using unstandardized gugulipid preparations have shown a more marked HDL effect, ranging from a 20-36% increase.[10] Notably, a randomized, placebo-controlled trial of 40 patients with TC of at least 275 mg/dL showed a 36% increase in HDL and a 22%

reduction in TC over 16 weeks of therapy.[11] This study used 4.5 g/d of purified gum guggulu, which is at least twice the dosage of gugulipid in other trials. While incidence of side effects was not mentioned, these results raise the possibility of a dose-response relationship.

Adverse Effects and Interactions

Phase I trials and clinical trials have found no significant untoward effects of gugulipid over 12 weeks of therapy.[8] In one study, several patients developed dyspepsia, hiccups, and bloating, but compliance was the same between drug and placebo (96%).[6] Additionally, there were no reports of liver, renal, glucose, or hematologic abnormalities. While there were no reports of muscle weakness, creatine phosphokinase was not measured.

There is one published report of drug interactions between gugulipid and both diltiazem and propranalol.[16] A single 1 g dose of gugulipid reduced the bioavailability of the two drugs by 35%. It is unclear whether this pharmacokinetic interaction translates into reduced clinical efficacy. Two anecdotal reports note a paradoxical pro-lipidemic effect.[17,18] It is unclear whether this effect represents non-responders (up to 30% of treated patients) or individual variations.

Formulation and Dosage

Resin, gums, and volatile oils comprise raw sap. In India, gugulipid extract is standardized to contain 50 mg guggulsterones/g and is sold under the trade name Guglip (Cipla Ltd.). The dosage best studied is 25 mg of guggulsterones po tid. Synthetic guggulsterones (compound 80/574) with better LDL reduction power are currently being evaluated in clinical trials in India.[10]

In the United States, gugulipid is available in a variety of preparations and is inexpensive. (*See Table.*)

Table

Cost and dosing comparisons of standardized gugulipid preparations vs. standard agents

Drug	Formulation*	Price#
Gugulipid (Preventics)	500 mg tid	$29.00
Gugulmax (Nature's Herb)	295 mg tid	45.00
Gugulipid C+ (BioTherapies, Inc.)	25 mg/ 20 mg vitamin C tid	27.25
Atorvastatin (Lipitor°)	10 mg qhs	54.72
Simvastatin (Zocor)	20 mg qhs	109.88
Pravastatin (Pravachol)	40 mg qhs	101.69
Gemfibrozil	600 mg bid	64.85
Cholestyramine	4 g bid	79.80
Niacin Extended Release (Niaspan)	2 g qhs	44.40
Niacin Short Acting	1 g bid	3.60

*Gugulipid standardized to provide 75 mg of guggulsterones/day.
#Price for 30-day supply. For gugulipid preparations, the suggested retail price is listed. For other drugs, the average wholesale price is listed.
°Statin doses are approximately equipotent.

Conclusions

Observations on gugulipid must be interpreted with caution since they are based on data from fewer than 200 patients. Standardized gugulipid extract at doses equivalent to 75 mg guggulsterone per day appears to be effective for mixed hyperlipidemia in approximately 70% of patients. Although gugulipid has never been directly compared to statins, it appears to reduce LDL on average by 17%, which is similar to 20 mg of fluvastatin or 10 mg of pravastatin.[14] Gugulipid also appears to increase HDL by 14%, which is similar to 1200 mg of gemfibrozil, and reduce TG by 24%, which is in line with the reduction from 2 g of niacin. A major advantage of gugulipid over currently available drugs is that adverse side effects have not been demonstrated.

Recommendation

Gugulipid might be considered for those mildly hypercholesterolemic patients who wish to attempt to avoid the side effects or expense of niacin, resins, and statins. Larger and longer randomized controlled trials of gugulipid in the primary prevention of cardiovascular disease are needed to confirm benefits and to establish the long-term safety of this promising Ayurvedic remedy. ❖

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Yoga as an Adjunct in the Long-Term Relief of Asthma

By Russell H. Greenfield, MD, FACEP

Currently, up to an estimated 15 million americans have asthma, and more than half were diagnosed with the disease before age 17.[1] In 1990, costs associated with asthma care alone were estimated to be $6.2 billion, or 1% of all U.S. healthcare costs that year.[2] In spite of the significant therapeutic advances witnessed in recent years, morbidity and mortality rates in industrialized nations have actually been increasing.[3]

Asthma is a chronic inflammatory disorder of the tracheobronchial tree. Its clinical appearance as airway obstruction occurs through a number of pathophysiologic processes. Some experts believe that exaggerated activity of the parasympathetic nervous system may have a negative influence on airway caliber and resistance. Emotional stress, in addition to other commonly noted physiologic triggers, is a recognized precipitant of asthma exacerbation.

Yoga, the Indian discipline said to enhance physical, mental, and spiritual health, has long been promoted in Europe and Asia as a useful adjunct in the treatment of asthma. With the practice of yoga gaining popularity in the United States, and with additional research examining its effects and use, more asthmatic patients are exploring its potential therapeutic benefits.

History and Culture

The discipline of yoga is thousands of years old and is an essential part of the practice of Ayurveda, one of the oldest complete medical systems in the world. Many ancient texts mention yoga, including the *Rig-Veda* (written approximately 4000 years ago), the *Upanishads* (scriptures of ancient Hindu philosophy), and the *Bhagavad Gita* (perhaps the most famous Hindu text).

Yoga was introduced to America at the 1893 Chicago World's Fair.[4] The word yoga is derived from a Sanskrit root meaning to yoke or unite, and the practice of yoga traditionally has been held to unite body, mind, and spirit in an attempt to enhance health and quality of life.

A common misconception is that yoga is a religious practice. Instead, yoga is a discipline of conscious living that encourages, but does not mandate, spiritual reflection. Yoga helps those who practice it to improve overall fitness and well-being. It can complement any religious or spiritual practice, or be practiced completely apart from one.

Technique

There are many different forms of yoga (*see page 128*) and many ways to practice the art, but perhaps the most common components of the discipline as taught in the United States are postures (asanas), breathing practices, and meditation.

The postures are designed to increase flexibility and to induce both physical and mental relaxation. There are literally thousands of asanas, but most people use only a few in their personal practice.

During the performance of these postures, great effort is made to concentrate on the breath. Breathing exercises (called pranayama) are performed both in association with asana practice and by themselves. The breathing exercises are seen as vital to the maintenance of health, and while most are intended to be deep and diaphragmatic, they need not be demanding. Breathing techniques are viewed as the foundation for meditative work.

Typical yoga sessions last for one hour and end with 5-20 minutes of meditation.

Yoga practice has traditionally been viewed as appropriate for anyone regardless of age or ability. The object of yoga practice is not competition, but to take the body from a place of discomfort to one of comfort by relaxing and strengthening it. Participants are instructed to practice slowly and carefully, and not to force their bodies or invite discomfort.

Yoga therapy has not been considered disease-specific in that distinct practices generally have not been taught only to patients with a particular malady. More prescriptive forms of yoga have become available only recently.

Types of Yoga

The ultimate goal of yoga is achieving health, comfort, and happiness. **Hatha Yoga**, the most commonly practiced yoga form in the United States, focuses on the physical and uses postures, breathing exercises, and meditation. The following types of Hatha yoga emphasize different paths:[4,18]

- **Astanga Yoga**—sometimes called "Power Yoga"—this form is only for those in good shape who are seeking an aerobic workout in addition to yoga's other benefits.
- **Iyengar Yoga**—stresses precision and allows props so that people can comfortably get into a given pose.
- **Kripalu Yoga**—uses a gentle, introspective approach. Poses are held a little longer than in other forms so that participants may focus on their mental/emotional states.
- **Restorative Yoga**—Postures requiring a minimum of effort are supported with props and held for 3-5 minutes.
- **Viniyoga**—uses a gentle, individualized approach that adapts to each participant's body type, as well as emotional and cultural needs. Postures are often combined with rhythmic movements of arms and legs.

Raja Yoga—also called "The Royal Path"—differs from Hatha yoga in that it emphasizes the meditative aspects of yoga, focusing on control of the intellect to attain enlightenment. ■

Mechanism of Action

Yoga's potentially therapeutic mechanisms have not been determined precisely. One of the most common explanations, not specific to asthma, is stress reduction with concomitant physical and psychological relaxation.

Physiologic changes associated with deep relaxation include diminished muscle tension, which allows for more efficient use of the diaphragm and thoracic musculature. Decreased oxygen use is also generally noted with various stress reduction techniques. These changes are consistent with an overall calming of autonomic tone,[5] which may manifest as a decrease in vagal efferent activity. The result is enhanced bronchodilation and diminished bronchial reactivity.

Another explanation, more specific to asthma, suggests that yoga practice may improve the mechanical aspects of breathing. The postures and breathing exercises used improve flexibility, massage the thoracic musculature, encourage increased tidal volume and decreased respiratory rate, and decrease bronchial reactivity. The end result is an increase in the efficiency of chest wall movement during the respiratory cycle.

Enhanced adrenocortical activity[6] has been reported in association with the practice of yoga, although the degree of enhancement has not been quantified. It is postulated that symptoms improve as a consequence of this increased activity and the resultant decrease in bronchial inflammation and hyperreactivity, as well as a blunted physiologic response to stress.

Clinical Studies

The majority of reports suffer from serious methodologic flaws. Many of the studies provide data on only a small number of patients, are uncontrolled, include confounding factors, and use various "cleansing procedures." Publication bias is also evident, as a thorough literature search failed to identify a single study in which yoga did not produce improvement or had a negative effect.

Several studies, however, are worth examining. One randomized, controlled study followed 106 asthmatic patients for a six-week period.[7] The 53 patients in the treatment group received training in postures, breath-slowing techniques, and meditation. Then, they were instructed to practice for approximately one hour each day. At randomization, the control group was felt to be equally as inclined toward the practice of yoga as the treatment group. At the end of the study period, the

treatment group experienced a significant decrease in the number of weekly asthma exacerbations, an increase in peak expiratory flow rate (PEFR), and a decrease in the amount of medication used.

The same authors also reported a parallel study of 570 patients who trained in and practiced yoga, and who were followed for periods ranging from 3-54 months.[8] They noted an improvement in PEFR and a significant decrease in the need for medication. Those who practiced regularly had the greatest improvement.

Khanam et al, in a pre-/post-period analysis trial, were able to show benefit for asthmatic patients after only one week of intensive training in postures, breathing techniques, and the underlying philosophy of yoga.[9] Subjects served as their own controls, ate a strictly vegetarian diet, and were maintained in an environment described only as one of "maximum relaxation." At the end of the trial there was no significant difference in FEV_1 or PEFR, but significant improvement was noted for peak inspiratory flow rate, breath holding time, and the degree of chest expansion. Resting heart rate decreased ($P < 0.05$), and patients reported an improved sense of overall well-being.

Another study used a randomized, double-blind, placebo-controlled, crossover design to evaluate the effects of pranayama breathing exercises on 18 patients with mild asthma (mean $FEV_1 = 3.2$ L).[10] All subjects initially practiced 15 minutes of slow, deep-breathing exercises twice a day for two weeks. During the active phase of the study, patients in the treatment arm used a device that imposes a 1:2 inspiration to expiration ratio equivalent to a form of pranayama breathing. The control group was provided a placebo device of similar appearance. At the end of the four-week trial, there was a significant decrease in bronchial reactivity, on the order of one doubling dose of histamine, in the group practicing pranayama. No other significant differences were found.

Singh previously noted a beneficial effect in a small, six-week study using the same device for patients with mild asthma and nocturnal wheezing.[11] Patients in this randomized, crossover trial used the device alone and in combination with warmed, humidified air. A beneficial effect on nocturnal wheezing and PEFR was noted at the end of the study. There was a slight trend toward improved results with combination therapy.

Adverse Effects

The practice of yoga is safe provided patients do not push themselves beyond their limits of comfort. The patient should be instructed to go the point of minimum tension and not to the point of stress. A sense of competition often leads to straining to maintain a pose and subsequent physical injury.

However, there are rare reports of disability related to the practice of yoga, including vertebral artery dissection,[12-15] persistent out-of-body experiences,[16] and the development of orbital varices.[17] Patients with known cerebrovascular insufficiency should be cautioned against prolonged head turning during yoga practice.

Prescription and Availability

Yoga requires commitment, both with respect to time and practice. The beginning student may choose to observe a class and the instructor before deciding whether to experience yoga.

No national standard for teacher certification exists, unfortunately, and credentials vary greatly. It is prudent to recommend that patients find a highly regarded instructor with at least four years of teaching experience. Prior to entering an open class, they should consider reserving a private session, which may cost from $25-45. During this pre-program evaluation, patients can advise the yoga teacher of any medical problems or injuries that might limit their ability to participate in the various aspects of the discipline. This will allow the instuctor to tailor a comfortable practice that does not compel the patient to compete with those more flexible or in better health.

Individual hour-long group classes cost approximately $6-8 each, but discounts are usually available when several classes are purchased. Ideally, one should develop a yoga practice that becomes a part of a regular daily routine.

Conclusion

Yoga is safe, affordable, and potentially beneficial to the asthmatic patient's health and sense of well-being. Whether that benefit is due to a direct effect on bronchodilation and inflammation or to a reduction in stress has yet to be determined. Yoga provides a sense of control and involvement in disease treatment that medications alone cannot offer. In the end, this may be the single most important reason to consider including yoga in the treatment plan for asthmatic patients.

Recommendation

While the scientific data to support the use of yoga is suggestive at best, there does appear to be support for consideration of its use as an adjunct for most stable patients with mild-to-moderate asthma. Our clinic experience also suggests that asthmatic patients who are motivated to decrease the use of medications, who believe that stress plays a significant role in their disease

process, and whose expectations support a positive response tend to have the greatest improvement in function and quality of life with a regular yoga practice. ❖

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CME Questions

26. Which of the following is *not* true:

a. Modern humans have osteoarthritis (OA) primarily in the medial compartment of the knee.
b. Weight loss is the single most effective treatment for OA of a weight-bearing joint.
c. More than four out of five persons older than the age of 65 show some clinical or radiological evidence of OA.
d. Glucosamine sulfate is a cure for OA.

27. In short-term controlled trials, glucosamine:

a. is effective in relieving pain and increasing range of motion in patients with OA.
b. was less effective at relieving pain than placebo.
c. is less effective than ibuprofen 400 tid in relieving pain from the second week onward.
d. has been proven to seek joint cartilage avidly.

28. Gugulipid appears to have pharmacologic properties that include:

a. inhibition of HMG-CoA reductase.
b. stimulation of lipolytic enzymes.
c. increased fecal excretion of sterols.
d. all of the above.

29. In most studies, gugulipid was found to reduce total cholesterol (TC) and triglycerides (TG) by:

a. TC: 20%, TG: 23%.
b. TC: 10%, TG: 15%.
c. TC: 40%, TG: 35%.
d. No effect

30. Regular yoga practice has been associated with:

a. enhanced adrenocortical activity.
b. an improved sense of well-being.
c. a calming of the autonomic tone.
d. all of the above.

31. Which of the following statements is true regarding the practice of yoga?

a. The physiologic basis for the therapeutic benefits of yoga are well-established.
b. The various components of yoga practice have been studied in isolation and have all been independently shown to be beneficial in treating asthma.
c. Relaxation and stress reduction appear to be important benefits.
d. The poses must be maintained no matter the discomfort to the individual.

With Comments from John La Puma, MD, FACP

Bodybuilding Supplement and CNS Depression

Source: LoVecchio F, et al. Butyrolactone-induced central nervous system depression after ingestion of RenewTrient, a "dietary supplement." *N Engl J Med* 1998;339:847-848.

A 36-year-old man was stopped by the police after he was seen to be driving erratically. The police found him to be lethargic, diaphoretic and vomiting. In the emergency department, a physical examination was unremarkable except for the appearance of inebriation. His vital signs were normal. His medical history was unremarkable; his ethanol level was 0; urinary screening for drugs of abuse was negative. The urine was positive for butyrolactone, as determined by gas chromatography and flame ionization detection. His mental status returned to normal within one hour, and the patient was discharged after six hours of observation. The FDA was notified.

Comment

The authors describe ingestion of the "bodybuilding supplement" RenewTrient, which contains gamma-butyrolactone, a solvent converted to gamma hydroxybutyric acid with water and sodium hydroxide. Sale of gamma hydroxybutyric acid has been banned by the FDA, but RenewTrient remains on the market and available in health food stores.

The patient described ingested 2 ounces of RenewTrient and drove a car 30 minutes later. A representative of RenewTrient research writes that the recommended dose is 1 ounce before a desired 3-6 hours of sleep, and that the effects "are quickly reversed by the administration of 2 mg of physostigmine."

The new RenewTrient label now reads, in part, "ensure that those around you are aware that you may be unarousable and that this is normal. A call for help may result in uninformed emergency medical personnel using expensive, unnecessary, and potentially dangerous methods of arousal."

It is uncertain whether RenewTrient "promotes the body's own natural production of growth hormone." It is certain that it is a potent central nervous system depressant, and can induce unarousable unresponsiveness or coma.

Recommendation

Gamma-butyrolactone is a dangerous "dietary supplement" that appears to induce coma. It is billed as a bodybuilding aid. Discourage its use. ❖

Mind-Body Medicine in Cancer Treatment

Source: Simonton SS, Sherman AC. Psychological aspects of mind-body medicine: Promises and pitfalls from research with cancer patients. *Altern Ther Health Med* 1998;4(4):50-67.

Research in psychosocial oncology has grown considerably. In this article, psychological interventions for cancer patients are reviewed. The following four areas are examined: adjustment and quality of life; symptom control; immune function; and disease progression. In each area, psychosocial dimensions of risk and resilience, the efficacy of current interventions, and the trajectory of future developments are considered.

Comment

This is a state-of-the-art review from two professors of behavioral medicine and otolaryngology at the University of Arkansas. They list and analyze more than 250 references, most of which are longitudinal descriptive studies and controlled clinical trials published in peer-reviewed journals.

Among other areas, the authors look at the evidence base for identifying those patients most vulnerable to psychosocial difficulties, and for those interventions designed to control nausea, vomiting, pain, and fatigue. Evidence for specific coping strategies and personality traits is also examined.

Overall, the authors find good evidence for improved quality of life from many interventions, from spirituality to biofeedback. There is less persuasive evidence for improved immune functioning and survival, but there is some, especially among already immunocompromised patients, the elderly, and those with endocrine-influenced tumors.

Recommendation

Because of its rigor and comprehensiveness, this is an invaluable work for clinicians and clinical researchers who treat and study patients with cancer. ❖

Riboflavin for Migraine Prophylaxis

Source: Schoenen J, et al. Effectiveness of high-dose riboflavin in migraine prophylaxis: A randomized controlled trial. *Neurology* 1998;50:466-470.

A deficit of mitochondrial energy metabolism may play a role in migraine pathogenesis. We found in a previous open study that high-dose riboflavin was effective in migraine prophylaxis. We now compared riboflavin (400 mg daily) and placebo in 55 patients with migraine in a randomized trial of three months duration. Using an intention to treat analysis, riboflavin was superior to placebo in reducing attack frequency ($P = 0.005$) and headache days ($P = 0.012$). The proportion of patients who improved by at least 50%, i.e., "responders," was 15% for placebo and 59% for riboflavin ($P =$

0.002) and the number-needed-to-treat for effectiveness was 2.3. Three minor adverse effects occurred—two in the riboflavin group (diarrhea and polyuria) and two in the placebo group (abdominal cramps). None was serious. Because of its high efficacy, excellent tolerability, and low cost, riboflavin is an interesting option for migraine prophylaxis and a candidate for a comparative trial with an established prophylactic drug.

Comment

In a rigorous, impressive, multicenter study funded by the Belgian Migraine Society, European investigators tried 400 mg of once daily oral riboflavin (vitamin B_2) on patients with migraines, with or without aura who had between two and eight attacks monthly, had no more than five days of interval headaches, no analgesic overconsumption and no serious organic or psychiatric disease. Women were required to have adequate contraceptive protection.

After three months, riboflavin dramatically reduced headache frequency and number of headache days but not headache intensity. Riboflavin did, however, take the full three months to have a significant effect.

Why should riboflavin work in helping to prevent migraine? Vitamin B_2 is a component of two co-enzymes and a precursor to the flavoenzymes that are involved in mitochondrial energy production in the brain. The vitamin may help patients reduce migraine attack frequency by increasing mitochondrial energy metabolism and with it, the intracerebral threshold for attacks.

The RDA (soon to be RDI) for riboflavin is 1.3-1.7 mg. Common food sources are organ meats, other meats, milk, eggs, and green vegetables. Grains, cereals, and flours are often fortified with riboflavin. For migraine prophylaxis, however, patients are better off with a supplement than with food; here, the vitamin functions as a medication, and without apparent side effect.

Recommendation

Consider recommending a three-month trial of riboflavin prophylaxis to patients who have two or more migraines monthly, and who want to avoid using beta blockers, valproate, and other prophylactic medications. ❖

Hidden Toxic Ingredients in Asian Patent Medicines

Source: Ko RJ. Adulterants in Asian patent medicines. *N Engl J Med* 1998; 339:847.

Asian patent medicines comprise herbs, plants, animal parts, and minerals, which are formulated into tablets, pills, or liquids for ease of use. However, many patent medicines manufactured in Asian countries contain toxic ingredients, such as heavy metals, as well as prescription drugs or unapproved ingredients that may or may not be identified on the label.

To establish a computer base for Asian patent medicines, to educate others, and to provide objective information about toxicity, the California Department of Health Services, Food and Drug Branch studied 260 Asian patent medicines collected from California retail herbal stores. Gas chromatography-mass spectrometry and atomic-absorption methods were used. At least 83 (32%) contained undeclared pharmaceuticals or heavy metals, and 23 had more than one adulterant.

Comment

Asian patent medicines smell of mystery and funk. Where are they from? The streets of urban Chinatown, especially in San Francisco, are layered with tables of boxed and sprawling produce. A little further in, sandals and ginseng roots from all parts of Asia, and dumplings stuffed with pork and bean paste carefully lifted from the steamer can be yours for little money.

Behind the tables, the sandals, and the dumplings are modern Chinese apothecaries filled with indecipherable scripts, teas of every imagining, cups for cupping and herbs for moxibustion and spleen dampness and infertility. Now, these herbs are wafting high above Chinatowns in San Francisco and Sacramento to Costcos and Sam's Clubs near you.

Of the 31 compounds which Ko, a PharmD and PhD, found to contain pharmaceutical ingredients, only 14 noted them on the label. Ephedrine, chlorpheniramine, methyltestosterone, and phenacetin were among those not listed.

Twenty-four products contained a median of 30 parts per million (ppm) of lead; 36 contained a median of 180 ppm of arsenic; 35 contained a median of 329 ppm of mercury. Ko notes that the U.S. Pharmacopeia "limits heavy metals in most oral pharmaceuticals to 30 ppm, with lower limits for lead, arsenic, and mercury."

Adulteration by synthetic and natural therapeutic and pathogenic substances of traditional Chinese medicines is commonplace. Such medicines have been reported as potential sources of mercury poisoning—and one studied medication contained 114,000 ppm of arsenic!

Recommendation

Physicians who counsel patients who seek to use traditional Chinese medicine made in Asia should warn them of the high prevalence of toxic ingredients. It is a safe bet that batch inconsistency is the rule here. Whether American manufacturers can do any better, assuming that there is something to do better with, remains to be seen. ❖

In Future Issues:

Selenium for Cancer Prevention
Acupuncture for Narcotic Addiction
Ginkgo for Adult ADD and Depression