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Vitamin E for Primary and Secondary Prevention of Heart Disease

By Matthew Sorrentino, MD, FACC

CORONARY ARTERY DISEASE IS THE LEADING CAUSE OF MORBIDITY and mortality in this country. Prevention of heart disease has focused on the recognition and treatment of classic and emerging risk factors that have been linked to the development of atherosclerotic disease and its complications. There is growing evidence suggesting that oxidative stress may play a role in the initial steps of atherosclerosis, and also may contribute to development of an unstable plaque. Antioxidant therapies may be useful in preventing both the initiation of atherosclerotic disease and its complications.

Pathophysiology

A crucial step in the development of atherosclerotic disease is the oxidation of LDL cholesterol. Oxidized LDL is taken up by macrophages via the scavenger receptor pathway to form foam cells, an integral part of the atherosclerotic plaque. In addition, oxidized LDL has many other potentially deleterious effects. (*See Table 1.*) Oxidized LDL is cytotoxic to endothelial cells causing endothelial dysfunction and inappropriate vasoconstriction. Endothelial dysfunction is a major cause of cardiac ischemia and underlies the complications of coronary disease including sudden cardiac death.

Mechanism of Action

Antioxidants have multiple potentially beneficial effects on coronary heart disease. The early prevention of LDL oxidation may prevent foam cell formation and the initial development of the fatty streak and early atherosclerotic plaques. In individuals with established atherosclerotic disease, antioxidants may improve endothelial function and prevent vasoconstriction and ischemic events. This in turn may help stabilize the atherosclerotic plaque reducing the chance of plaque rupture and an acute coronary thrombosis.

Animal Studies

Primary Prevention of Atherosclerosis. Experimental studies have linked antioxidants with decreased atherosclerosis in animals. In these studies, antioxidants usually were administered before the development of atherosclerosis suggesting that the decrease in LDL

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oxidation may have reduced foam cell production and plaque formation.[1]

Clinical Studies

Primary Prevention. Epidemiological data suggest that a dose of at least 100 mg/d vitamin E has a protective effect against coronary events.

The Nurses' Health Study evaluated vitamin E supplementation as reported on questionnaires completed by more than 80,000 nurses. The group of nurses taking the largest amount of vitamin E had a lower risk of coronary events than those taking the lowest amount.[2] The Health Professionals' Follow-up Study found similar results in men with the highest vitamin E intake.[3]

There are minimal prospective primary prevention data from available studies to determine if vitamin E is an effective preventive agent for the development of coronary events. The only completed primary prevention trial is the alpha-tocopherol, beta-carotene cancer prevention study designed to evaluate the development of lung cancer in a cohort of Finnish male smokers.[4] Coronary outcomes were evaluated in a subgroup of men who were randomized to either placebo or 50 mg of vitamin E. After a median of 6.1 years there was no statistically significant difference in the incidence of nonfatal myocardial infarction in the vitamin E group compared to placebo. There was a trend for a decrease in fatal coronary events (8% decrease, confidence interval -19% to 5%) in the vitamin E group but it was not statistically significant. The dose of vitamin E used in this study, however, may have been too small to achieve a benefit.

Secondary Prevention Trials. In patients with established coronary artery disease, antioxidants may improve endothelial function, reduce ischemia, and stabilize atherosclerotic plaques to prevent plaque rupture. The Cambridge Heart Antioxidant Study (CHAOS) was a prospective trial of vitamin E (400-800 IU) in patients with established coronary heart disease.[5] The risk of the primary endpoint (a combination of death and nonfatal myocardial infarction) was reduced by 47% in the vitamin E group. There was no reduction in cardiovascular death in the vitamin E group. This study used significantly higher doses of vitamin E than had been studied previously.

The results of the CHAOS trial, however, have not been reproduced by two recently reported large trials, the Heart Outcomes Prevention Evaluation (HOPE) study and the GISSI-prevention trial. The HOPE study enrolled 2,545 women and 6,996 men at high risk of cardiovascular events because of the presence of previously diagnosed cardiac disease or diabetes mellitus with at least one other major risk factor.[6] Patients were randomized to receive 400 IU of vitamin E from natural sources or an equivalent placebo for four to six years. There was no difference between the groups in the number of deaths from cardiovascular causes, myocardial infarctions, stroke, or hospitalizations for unstable angina or heart failure.

Why did this well-done prospective, randomized, controlled trial show no benefit when the epidemiological trials suggested benefit? Two main possibilities: First, vitamin E may need to be given with additional antioxidants to work as cofactors for a beneficial effect. This study used vitamin E alone as a supplement. And second, vitamin E may give benefit only early in the disease process (primary prevention) but not after significant disease is already established, as in the HOPE patients.

The GISSI-prevention trial investigated the effects of vitamin E and omega-3 fatty acids on cardiovascular events in individuals who already have suffered a first myocardial infarction.[7] Vitamin E was given as a 300 mg capsule of synthetic alpha-tocopherol. All patients were also on a Mediterranean-type diet. In comparison with the placebo group, there was no effect on cardiovascular endpoints noted in the vitamin E group.

Why was GISSI also a negative study? There are

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
EDITORIAL GROUP HEAD: Leslie G. Coplin.
MANAGING EDITOR: Kevin New.
GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $38 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Subscription Prices

United States
$279 per year (Student/Resident rate: $115).
Multiple Copies
1-9 additional copies: $206 each; 10 or more copies: $183 each
Outside the United States
$309 per year plus GST (Student/Resident rate: $130 plus GST).

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Alternative Medicine Alert has been approved by the American Academy of Family Physicians as having educational content acceptable for Prescribed credit hours. Term of approval covers issues published within one year from the beginning distribution date of July 1, 2000. This volume has been approved for up to 24 Prescribed credit hours. Credit may be claimed for one year from the date of this issue.
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Table 1

Deleterious effects of oxidized LDL cholesterol

1. Formation of foam cells via the scavenger receptor pathway
2. Cytotoxic to endothelial cells causing endothelial dysfunction
3. Chemoattractant for monocytes
4. Enhance binding of monocytes to endothelial cells
5. Inhibits macrophage migration
6. Promotes vasoconstriction
7. Increases platelet aggregation
8. Increases tissue factor secretion

three key possibilities. The Mediterranean-type diet may have given an antioxidant beneficial effect that was overlapped by additional vitamin E supplementation. Second, the dose of vitamin E used in this study is lower than used in the CHAOS trial, and may have been inadequate to achieve a cardiovascular effect. And third, synthetic vitamin E supplementation—which may not have the same biologic equivalency as natural, mixed vitamin E—was used.

These two recent secondary prevention vitamin E studies raise important concerns about the use of vitamin E to prevent subsequent cardiac events, especially in individuals with established coronary artery disease. The amount of vitamin E used in these studies exceeds an easily obtainable daily dose through diet alone and should have had an impact on cardiac events if this therapy is indeed effective. These studies do not address primary prevention, however, and it remains possible that the early use of vitamin E may prevent initial plaque formation. Ongoing primary prevention studies may clarify this issue.

Secondary Prevention in Renal Patients

Chronic hemodialysis patients are known to have a high cardiovascular mortality rate thought to be caused, in part, by enhanced oxidative stress. Recently a small trial in patients with end-stage renal disease treated with hemodialysis was completed. The results suggest a benefit of vitamin E in this high-risk group of patients.[8]

In this study, 196 hemodialysis patients with preexisting coronary artery disease were assigned to receive 800 IU/d vitamin E or placebo and were followed for two years. The primary endpoint (a combination of fatal and nonfatal myocardial infarction, ischemic stroke, peripheral vascular disease, and unstable angina) occurred in 16% of the vitamin E group compared with 33% of the placebo group. The only individual endpoint that reached significance was myocardial infarction: five patients receiving vitamin E and 17 assigned to placebo had a myocardial infarction. Two deaths associated with hemorrhage occurred in the vitamin E group. Although this was not statistically significant, vitamin E is known to inhibit protein kinase C and is associated with an increased risk of bleeding.

The benefit of vitamin E in this study may have occurred because the cohort of patients was at higher risk than patients in the other vitamin E studies, and because hemodialysis patients are known to have evidence of greater oxidative stress. More work will need to be done to define other populations of patients likely to benefit from antioxidant therapy.

Formulation and Dosage

Vitamin E, a fat-soluble vitamin contained in vegetable, nut, and seed oils, exists as at least eight naturally occurring compounds, all of which have antioxidant activity.[9] Alpha-tocopherol is the most active component. Dietary vitamin E usually is expressed as mg of alpha-tocopherol equivalents or in an older designation, IUs (international units). One IU is equivalent to approximately 1 mg of dl-alpha-tocopheryl acetate.[10] A well-balanced, Mediterranean-type diet should supply about 8-12 IU/d of vitamin E. (*See Table 2 for food sources.*)

Epidemiological data, derived from studies of synthetic dl-alpha-tocopherol, suggest that at least 100 mg/d are needed to derive protection against coronary events.

Adverse Effects and Interactions

Tocopherols inhibit platelet aggregation in vitro and may interfere with vitamin K-dependent coagulation and, therefore, may cause bleeding when used alone or in conjunction with other antiplatelet agents like aspirin or NSAIDs and with coumadin. Both the HOPE and GISSI trials, using up to 400 mg/d of alpha-tocopherol, did not show excessive bleeding risk.

Conclusion

Vitamin E is an antioxidant vitamin that may help prevent the oxidation of LDL cholesterol and the development of atherosclerosis. The use of vitamin E in patients with established coronary heart disease, however, has not been shown to reduce cardiovascular events. There still may be a role for vitamin E in primary prevention to prevent early plaque development, but more studies are needed to clarify this use.

Recommendation

Vitamin E currently cannot be recommended as therapy for secondary prevention. There may be subgroups of patients, however, such as cardiac patients on chronic

Table 2

Food sources of vitamin E

Food	Amount	Vitamin E (mg)
Wheat germ oil	1 tablespoon	37.2
Sunflower seeds	1/4 cup	26.8
Wheat germ, raw	1/4 cup	12.8
Almonds/hazelnuts	1/4 cup	12.7
Pecan halves	1/4 cup	12.5
Safflower oil	1 tablespoon	7.9
Peanuts	1/4 cup	4.9
Corn oil	1 tablespoon	4.8
Peanut butter	2 tablespoons	3.8
Soybean oil	1 tablespoon	3.5
Cod-liver oil	1 tablespoon	3
Lobster	3 oz	2.3
Salmon, fillet	3 oz	0.6

Source: Reproduced with permission from La Puma J, Becker J. *CHEF Clinic: Cooking with Antioxidant Vegetables*. Elk Grove Village, IL: 2000; 10.

hemodialysis, who may benefit from antioxidant therapy. The potential for an increased risk of bleeding complications needs to be considered before recommending this therapy. The benefit for primary prevention has yet to be determined although there are good theoretical reasons why vitamin E may prevent LDL oxidation and the development of atherosclerosis. Supplemental vitamin E of at least 400 IU can be considered in individuals at increased risk for but who do not yet have heart disease. ❖

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Garcinia cambogia for Weight Loss

By Michael D. Cirigliano, MD, FACP, and Philippe O. Szapary, MD

OBESITY HAS BEEN AND CONTINUES TO INCREASE AS A significant health problem in the United States. According to data from the National Health and Nutrition Examination Surveys (NHANES III), the prevalence of overweight individuals in the U.S. population has increased by 8% from 25% to 33% over the past 10 years.[1] Given this epidemic, numerous attempts have been made to address this problem including fad diets, prescription medications, surgery, and behavior modification. Many obesity therapies have been found to be ineffective over the long term and in some cases have even led to harm.[2] This has led many to look for "natural" diet aids thought to be safer and not having the same risks as surgery and/or pharmaceutical agents. These natural substances have included guarana, ephedra, chromium, carnitine, psyllium, chitosan, conjugated linolenic acid, DHEA, and dandelion to name a few. *Garcinia cambogia* has become one of the most popular and highly marketed natural products utilized for the treatment of obesity.

Background: Overweight and Obesity

An estimated 97 million U.S. adults are overweight or obese, a condition that substantially raises their risk of morbidity from hypertension, dyslipidemia, type 2 diabetes, coronary heart disease, stroke, gallbladder dis-

ease, osteoarthritis, sleep apnea, and endometrial, breast, prostate, and colon cancers.[3]

Obesity is defined as having a body mass index (BMI) of ≥ 30 kg/m^2. Recent data indicate that the prevalence of obesity has increased from 12% in 1991 to 17.9% in 1998.[4] Obesity is a multifactorial chronic disease that develops from an interaction of genetics and environment. In 1996, the Food and Drug Administration for the first time approved a medication, dexfenfluramine, for long-term treatment of obesity. However, in 1997, valvular heart disease appeared in a significant number of persons who took dexfenfluramine, the d-isomer of fenfluramine, especially in combination with phentermine.[5] This experience has raised concern over the long-term use of any anti-obesity medications. Even newer and apparently safer medications, including sibutramine and orlistat, promise only modest weight loss. Because of their prescription status and high cost, these medications may have a minimal effect on the general population. The limited success and potential complications of these pharmacologic weight loss aids has led to a large and growing market for alternative therapies such as herbal products.[6] Garcinia is one such agent that has been the subject of significant clinical interest and scientific study.

Source and Identification

Garcinia is found and grown primarily in Southeast Asia. The dried and cured pericarp, or rind, of the fruit of this species contains up to 30% by weight of (-)-hydroxycitric acid (HCA)[7] and is considered the active compound for weight loss. A member of the Clusiaceae family, it is also commonly known as brindle berry. Rinds of the fruit traditionally are used in regional cooking practices and are noted to make meals more filling.[8] Historically, garcinia has been used for dysentery, as a purgative, and for treatment of worms and parasites, in addition to its use for weight loss.[9] Garcinia has a sour taste and is used extensively as a "souring agent" in traditional Indian cuisine.

Mechanism of Action

Garcinia is believed to have a multifactorial effect on promoting weight loss. This is thought to occur through suppression of de novo fatty acid synthesis, increased lipid oxidation, and reduced food intake.[10] The effect of enhanced satiety may account for the decrease in food consumption.[6] Early satiety effects may be caused by inhibition of ATP citrate lyase, which limits the availability of acetyl coenzyme A (acetyl CoA) for lipid synthesis during carbohydrate feeding. Carbon then is diverted to glycogen synthesis. It is thought that glycogen levels serve as a primary signal for energy regulation.[11] However, this concept is controversial.[12]

The anorectic effects of garcinia may be caused by reductions in acetyl CoA; malonyl CoA levels also are depressed reducing negative feedback on carnitine acyltransferase.[13] This results in increased lipid transport into the mitochondria and inefficient oxidation with ketone body formation.[6] Ketones are appetite suppressants. This mechanism also is controversial as an association between hunger levels and ketosis has not been observed.[14] Some have also theorized an effect on the hypothalamic satiety center.

Animal Studies

In one study, garcinia's effects on the metabolic rate of mice was studied in a placebo-controlled trial.[15] In this study, mice were placed into metabolic chambers and administered 10 mg of garcinia or water orally. Serum-free fatty acid levels were significantly higher 100 min after administration in the garcinia-treated group, but the respiratory exchange ratio was not different between the groups. The concentration of glycogen in the gastrocnemius muscle was higher in the treated group 16 hours after administration. Maximum swimming time until fatigue was slightly longer in the treatment group. Results suggested that chronic administration of garcinia promotes lipid oxidation and spares carbohydrate utilization in mice at rest and during running.

In another animal study, several animal models were used to observe changes in obesity with use of garcinia.[16] In this study, the mature rat, the gold thioglucose-induced obese mouse, and the ventromedial hypothalamic lesioned obese rat had reduced food intake and body weight gain when given a chronic nontoxic dose of garcinia. Body composition analyses of mature rats treated with garcinia demonstrated a significant depression of body lipid levels and an unaltered body protein content. However, the authors did not find any statistically significant effects on weight gain, food intake, or body lipid or protein levels when compared to controls.

Another study examined the effects of administration of garcinia on the accumulation of lipid in the meal-fed rat by examining the rates of lipogenesis after acute and chronic treatment.[17] Oral HCA administration significantly depressed the in vivo lipogenic rates in a dose-dependent manner in the liver, adipose tissue, and small intestine over an eight-hour period. Control animals demonstrated elevated rates of lipid synthesis. Rats receiving garcinia consumed less food than the untreated controls.

Clinical Studies

A number of clinical trials have attempted to identify

the safety and efficacy of garcinia for weight loss. Although there have been intriguing, scientifically sound animal studies and theoretical findings, studies in humans have been limited and results have been contradictory. Most studies showing a positive effect have been limited by small sample sizes, utilized combination products, lacked placebo control, and used inaccurate measures of body lipid change.[18]

In one placebo-controlled trial, the effect of garcinia on suppression of hunger was evaluated in 89 mildly overweight females.[6] These subjects were prescribed 5,020-kJ diets for 12 weeks as part of a double-blind, placebo-controlled study. Forty-two participants ingested 400 mg caplets of garcinia 30-60 minutes prior to meals for a total dose of 2.4 g/d (1.2 g/d HCA). Forty-seven participants ingested matched placebos. Weight and body composition were assessed at baseline and every other week for 12 weeks. Food intake and appetitive variables were assessed at baseline and monthly for 12 weeks. Both groups lost weight with the treatment group achieving a significantly greater reduction (3.7 ± 3.1 kg vs. 2.4 ± 2.9 kg). Hunger and garcinia ingestion, however, were unrelated. The authors concluded that garcinia does not work through a satiety mechanism.

In the largest and most rigorously conducted trial, 135 overweight men and women subjects were randomized to receive either active herbal compound (1,500 mg/d HCA) or placebo, and both groups were prescribed a high-fiber, low-energy diet for 12 weeks.[19] Body weight was evaluated every other week and fat mass was measured at weeks 0 and 12. Patients in both groups lost a significant amount of weight during the 12-week treatment period ($P < 0.001$); however, between-group weight loss differences were not statistically significant (mean SD, 3.2 ± 3.3 kg vs. 4.1 ± 3.9 kg; $P = 0.14$). There were no significant differences in estimated percentage of body fat mass loss between treatment groups. The fraction of subject weight loss as fat was not influenced by the treatment group. Garcinia failed to produce significant weight loss and fat mass loss beyond that observed with placebo.

This study and its conclusions have been criticized for a variety of reasons.[20] It has been noted that for garcinia to be effective it must be coadministered with a simple carbohydrate-rich (lipogenic) diet. This study utilized a high-fiber diet with 20%, 50%, and 30% of energy as fat, carbohydrate, and protein, respectively. A high-fiber diet may, in fact, reduce gastrointestinal absorption of HCA. This is important because HCA must be present inside the target cell to inhibit the intracellular enzyme adenosine triphosphate (ATP)-citrate-lyase.

Additional criticisms have been made of the low-energy diet, which may have limited HCA's conversion of citrate to acetyl-CoA by ATP-citrate-lyase.[21] This conversion occurs only when the rate of glycolysis exceeds the body's energy requirements. If the body's energy needs are not met, the Krebs cycle converts carbohydrate calories into ATP for energy rather than citrate for fatty acid synthesis. This, therefore, would limit the ability of HCA to be effective.

In another clinical trial, 10 sedentary adult males aged 22-38 with BMIs of 22.4-37.6 kg/m^2 were enrolled in a randomized, double-blind, placebo-controlled, crossover study involving three days of HCA (3 g/d) or placebo supplementation.[22] Protocol A involved treatment and placebo arms with no exercise and Protocol B involved treatment and placebo arms with moderately intense exercise. Energy expenditure and respiratory quotient were measured for 150 minutes following overnight fast. Blood samples were collected for the determination of glucose, insulin, glucagons, lactate, and beta-hydroxybutyrate concentrations.

In a fasted state and following three days of HCA treatment, respiratory quotient was not significantly lowered during rest or during exercise when compared to placebo. Energy expenditure was not affected. Blood substrates measured were not different between treatment groups. The authors concluded that this study did not support the hypothesis that HCA alters the short-term rate of fat oxidation in the fasting state during rest or moderate exercise.

Adverse Effects and Drug Interactions

No reported adverse effects or drug interactions have been reported in the literature. Given a lack of safety data, garcinia's use during pregnancy and lactation is contraindicated.

Formulation and Dosage

At least 14 over-the-counter garcinia products are available to consumers. Many preparations are combination products containing other agents including chromium, ephedra, guarana, and *Iris versicolor*. Typical dosages are 1,000 mg tid with extracts containing 50% HCA.[23] Calcium, common in many HCA products, can further reduce solubility and also may hinder bioavailability.[24]

In many herbal weight loss preparations, combinations of herbal agents, such as guarana and ma huang, are utilized regularly. These have documented serious side effects, have the potential for exacerbating hypertension and arrhythmias, and have been shown to have minimal efficacy.

Conclusion

The limited placebo-controlled, scientifically sound research assessing garcinia's effectiveness as a weight loss agent fails to provide positive evidence. Fortunately, garcinia appears to be safe over the short term. However, randomized controlled trials in obese patients on high carbohydrate diets with larger doses of garcinia are needed to further assess the therapeutic potential of this ayurvedic herb.

Recommendation

Based on the present data, the use of garcinia for weight loss cannot be recommended. It is important to advise patients to avoid combination products that might contain stimulants, such as ma huang and guarana, which have been associated with serious adverse cardiovascular outcomes. Patients should be referred to a medically sound weight management program for assistance with the skills needed to change eating and fitness habits. ❖

Dr. Cirigliano and Dr. Szapary are Assistant Professors of Medicine at the University of Pennsylvania School of Medicine in Philadelphia.

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Qigong for Complex Regional Pain Syndrome

By V. Jane Kattapong, MD

Who except the gods can live time through forever without any pain?

Aeschylus
Prometheus Bound

COMPLEX REGIONAL PAIN SYNDROME (CRPS), ALSO known as reflex sympathetic dystrophy or sympathetically mediated pain, is a poorly understood pain syndrome that often is refractory to medical management. CRPS typically begins after an injury, usually involving the distal extremities.[1] Often the inciting injury is a bony fracture. A wide variety of other factors have been reported to potentiate CRPS, including soft tissue injury, venipuncture, intramuscular injection, dental extraction, casts, medications, myocardial or cerebrovascular ischemia, carcinoma, osteomyelitis, multiple sclerosis, spondylosis, seizures, and peripheral neuropathy.[1] After the initial insult, an intense burning, throbbing, or aching pain develops in a region that often involves a much greater area than was initially injured. Signs of vasomotor instability, including swelling, sweating, and color and temperature changes, typically develop.[2]

Treatment of CRPS

Early mobilization of injured extremities decreases the incidence of reflex sympathetic dystrophy.[3] If CRPS does develop, physical therapy helps relieve pain and maintain range of motion. Pharmacologic treatment options include alpha- and beta-blockers to inhibit local sympathetic output and modulate vasomotor tone. Calcitonin is beneficial in about 60% of patients, via an unknown mechanism.[1] Medications that combat neuropathic pain syndromes also may be beneficial; these include tricyclic and tetracyclic antidepressants and antiepileptic agents. Non-steroidal anti-inflammatory agents, prednisone, and lidocaine patches all have a place in the pharmacologic armamentarium for this disorder as well.[4] For patients who respond incompletely to these medications, sympathetic blocks may offer temporary relief.

While early treatment with sympathetic blockade or pharmacologic therapy may provide relief in early-stage CRPS, treatment of late-stage CRPS is much more problematic.[5] Late-stage CRPS is regarded as generally being refractory to traditional modalities of pain therapy. Consequently, late-stage CRPS lends itself well to therapeutic trials of complementary or integrative therapeutic modalities, such as traditional Chinese medicine (TCM).

What is Qigong?

Qigong is one form of TCM. *Qi* means vital energy, and *gong* means training. Qi is composed of yin and yang, or negative and positive energy. TCM practitioners believe that when yin and yang are not in equilibrium, illness may occur.[5] The Qigong Association of America describes qigong in the following way: "Qigong is a self-healing art that combines movement and meditation. Visualizations are employed to enhance the mind/body connection and assist healing."[6] According to the National Qigong Association, qigong is a 3,000-year-old Chinese healing practice that is based on the precept: "Stagnation equals illness. Movement creates wellness."[7]

The principles upon which the practice of qigong was founded include the belief that the sensation or feeling of poor physical or emotional health is correlated with inadequate movement of the body, mind, and spirit. Traditional qigong practitioners incorporated forms of physical movement such as dance to alter their own energy or qi.[7] As qigong principles and practice evolved, simple dance became replaced with specific patterns of movement, breathing, and meditation. According to the Qigong Association of America, "Regular practice of qigong can: prevent and treat illness, reduce stress—establish balance, integrate mind/body/spirit—bring peace."[6]

The Practice of Qigong

Qigong can be practiced at any time or any place, while sitting, standing, lying, or walking. It can be practiced for as little as a few minutes at a time or for longer amounts of time. Thus, few spatial or temporal requirements are needed for the practice of qigong.[8] In comparison to Tai Chi, which incorporates physical movement and meditation, qigong utilizes breathing techniques and meditation to promote internal movement. Thus, to an outside observer, an individual engaging in qigong might not appear noticeably different from an individual standing quietly.

Qigong and Physiological Parameters

Although the reproducibility of these results is unclear, qigong exercise has been reported to produce alterations in many physiological parameters. Qigong exercise has been reported to alter neurotransmitter levels, cardiovascular parameters, joint pain, and muscle spasm; vasoconstriction also has been reported.[9-13]

Controlled Trial of Qigong and CRPS

Methods. Few rigorously gathered data have been published about qigong and CRPS. In the one random-

ized study, 26 patients with intractable CRPS, ranging in age from 18 to 65 years of age, were recruited to participate in a 10-week, blinded protocol.[5] The patients received either actual qigong training or sham qigong training. Diagnostic criteria for study inclusion included the requirement that at least five of the following attributes were present:

1. Positive three-phase bone scan;
2. Burning pain;
3. Allodynia (cold or mechanical);
4. Swelling of the affected extremity;
5. Mottling of the skin;
6. Dystrophy of skin and/or muscle;
7. Negative diagnostic sympathetic blockade.

All patients were classified as treatment failures, defined as failure to experience 50% reduction in pain through conventional pharmacologic therapy, physical therapy, or chiropractic therapy.

Patients assigned to the treatment group received six biweekly, 40-minute training sessions from a recognized qigong master. The sessions included exposure to qigong musical compositions and art, as well as qigong exercise. Patients in the control group received simulated training sessions with an instructor who was not a qigong master. The sham instructor was an individual of Asian descent. These patients viewed abstract art images and listened to non-qigong influenced music.

After the completion of these sessions, each group was asked to practice the techniques and exercises that they had been taught for seven additional weeks.

Outcome Measures. At the time of study entry, all participants completed a series of evaluations, including a comprehensive history and physical exam, diagnostic testing such as three-phase bone scan, a 90-item symptom check list, a test of responsiveness to suggestions, and an evaluation of patient expectation.[5]

Monitoring of patients occurred during weeks one, three, six, and 10. Outcome measures that were utilized included thermography (assessment of skin surface temperatures), range of motion of the affected limb, physical findings, response to pain intensity rating scales, medication usage, behavioral assessment via a subscale of the Sickness Impact Profile, determination of frequency of night-time awakening caused by pain, mood assessment via the Beck Depression Inventory, and an assessment of anxiety level. In addition, participants were asked to complete a 10-point rating scale regarding their level of confidence that they had been assigned to the treatment group rather than the control group.

Results. Eleven patients completed the protocol in each of the two groups. Participants in both the treatment and control groups tended to believe they were participating in the treatment group: On a 10-point scale with 10 indicating complete confidence in having participated in the treatment group, the mean score for qigong participants was 7.9 and the mean score for control group participants was 6.2. There was no statistically significant difference in the scores of these two groups.

There was no statistically significant long-term difference between the two groups in pain intensity rating on a visual analog pain scale. However, an analysis of variance including the variables group membership (qigong or control), treatment session (session 1 or session 6), and time of assessment (before or after session) demonstrated a significant two-way interaction of group membership with time of assessment, suggesting that a temporary improvement in pain perception may occur during qigong performance.[5]

There were no statistically significant differences between the treatment and control groups in scoring of physical indicators including swelling, skin discoloration, dystonia, dystrophic changes, joint range of motion, or thermography. In addition, no statistically significant differences were found between groups in a behavioral assessment using the Sickness Impact Profile.[5] However, the mood assessment evaluation suggested that all participants experienced less anxiety with time, and that participants who received qigong training experienced less anxiety than those who did not.[5]

Table 1

Factors associated with the development of CRPS

Bony fracture of the distal extremities
Soft tissue injury
Venipuncture
Intramuscular injection
Dental extraction
Casting
Medications
Myocardial ischemia
Cerebrovascular ischemia
Carcinoma
Osteomyelitis
Multiple sclerosis
Spondylosis
Seizures
Peripheral neuropathy

Side Effects

Although Wu et al did not report side effects in the group of patients studied, other sources have reported mental side effects, ranging from serious mental disor-

ders to mild mental symptoms. These have included qigong-induced or qigong-precipitated psychosis. It has been suggested that psychosis only occurs in individuals predisposed to development of this disorder.[14] Mild symptoms have included the experience of transient illusions or "pseudohallucinations"[15] and alterations in perception, thinking, and behavior.[16]

Conclusion

The only study of qigong and CRPS has notable limitations. Small numbers of patients participated, the randomization procedure was unclear, the control group differed from the treatment group in terms of gender distribution, and the trainers were not blinded. Thus, the finding that qigong training may give rise to short-term perceived decreases in pain intensity in patients with late-stage CRPS, and may result in long-term reduction in anxiety in these patients, cannot be confirmed. On the other hand, qigong's long tradition, simplicity, ease, and structure are appealing and warrant further study.

Recommendation

Since only a few transitory side effects have been reported to be associated with qigong, and one limited controlled study has suggested some beneficial effects, it appears that qigong may be recommended appropriately as a useful therapeutic modality for most patients with end-stage CRPS. However, patients who are predisposed to the development of psychotic symptoms should engage in this technique with caution or not at all. ❖

Dr. Kattapong is a board-certified neurologist and a principal in MediCat Consulting, a health services consulting firm in Tucson, AZ.

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Note to Readers

American Health Consultants is pleased to introduce a new quarterly addition to *Alternative Medicine Alert: Alternative Medicine Reports*, edited by David Schiedermayer, MD, FACP, Professor of Medicine at the Medical College of Wisconsin in Milwaukee. These monograph-style articles will cover a variety of complementary and alternative therapies for a specific indication. We would like to hear your feedback on this new feature. Please contact Leslie Coplin at (404) 262-5534 or e-mail: leslie.coplin@ahcpub.com. ❖

CME Questions

20. Clinical trials have found that in patients with established coronary heart disease, vitamin E:
a. prevents the oxidation of LDL cholesterol.
b. prevents the development of atherosclerosis.
c. has not been shown to reduce cardiac events.

21. High doses of vitamin E may cause bleeding when taken:
a. alone.
b. with antiplatelet agents (aspirin, non-steroidal anti-inflammatory agents).
c. with coumadin.
d. All of the above
e. None of the above

22. Parts of *Garcinia cambogia* utilized medicinally are:
a. Rinds of the fruit
b. Bark
c. Roots

23. Which of the following factors may potentiate the development of complex regional pain syndrome (CRPS)?
a. Bony fracture
b. Venipuncture
c. Multiple sclerosis
d. All of the above

24. CRPS patients who practiced qigong experienced:
a. long-term decreases in pain intensity.
b. short-term decreases in pain intensity.
c. improvements in skin discoloration.
d. improvements in range of motion.

Clinical Briefs

With Comments from John La Puma, MD, FACP

Vitex agnus-castus for Premenstrual Syndrome Symptoms

Source: Schellenberg R. Treatment for the premenstrual syndrome with agnus castus fruit extract: Prospective, randomised, placebo controlled study *BMJ* 2001;322:134-137.

TO COMPARE THE EFFICACY AND TOLerability of agnus castus fruit (*Vitex agnus-castus* L extract Ze 440) with placebo for women with premenstrual syndrome, we conducted a randomized, double-blind, placebo-controlled, parallel-group comparison over three menstrual cycles.

We used general medicine community clinics in the UK. We screened 178 women, and evaluated 170 (active 86; placebo 84). Subject mean age was 36 years; mean menstrual cycle length was 28 days; mean duration of menses was 4.5 days. We gave one tablet daily of agnus castus (dry extract tablets) or matching placebo for three consecutive menstrual cycles.

For our main variable, we measured change from baseline to endpoint (end of the third menstrual cycle) for the following self-assessed parameters: irritability, mood alteration, anger, headache, breast fullness, and other menstrual symptoms including bloating. For our secondary variable, we measured changes in clinical global impression (severity of condition, global improvement, and risk or benefit) and responder rate (50% reduction in symptoms).

Our results show improvement in the main variable was greater in the active group compared with placebo group ($P < 0.001$). Analysis of the secondary variables showed significant ($P < 0.001$) superiority of active treatment in each of the three global impression items. Responder rates were 52% and 24% for active and placebo, respectively. Seven women reported mild adverse events (four active; three placebo), none of which caused discontinuation of treatment. We conclude that dry extract of agnus castus fruit is an effective and well-tolerated treatment for the relief of premenstrual syndrome symptoms.

COMMENT

Vitex agnus-castus is approved in Germany for use in disorders of the menstrual cycle, premenstrual syndrome, and mastodynia.

Five of the six self-assessment items (irritability, mood alteration, anger, headache, and breast fullness) were positive for vitex users. Analyses of subgroups—women who were taking oral contraceptives and screened women without post-baseline values—did not change the results.

This study is probably the best randomized, double-blind, controlled trial to date in this area. The authors applied DSM diagnostic criteria strictly, and used robust, validated, disease-specific instruments of assessment. The decision to test vitex against a placebo instead of an intervention is reasonable, given the high placebo response in this disorder and the modest effectiveness of vitamin B_6, calcium, and other interventions. Though it is unclear how 91 patients were randomized to the active arm and 87 to placebo, given randomization in blocks of four, the authors minimized clinic visits to minimize bias from medical reassurance. The dosage was modest (active fruit extract ZE 440: 60% ethanol m/m, extract ratio 6-12:1; standardized for casticin; 20 mg/d) and there were few subjects lost to follow up, unlike other trials in this area.

The authors speculate that the mechanism of action also may be related to modulation of stress-induced prolactin secretion via dopamine, without directly affecting luteinizing hormone or follicle-stimulating hormone.

Adverse events were insignificant and not different between the two groups.

The author's conclusion that vitex is effective in the treatment of the premenstrual syndrome, confirmed by women's self-assessment and by the doctors' evaluation, appears to be evidence-based. More than half the women had a 50% or greater improvement in their symptoms. As is the case for many studies of prescription pharmaceuticals, Zeller AG,

Switzerland, supplied the study medication and sponsored the study.

Klepser and Nisly report, "The chaste tree berry gets its name from the belief that the plant would inspire chastity. To help with chastity, monks would eat the berries or seeds as a spice to decrease sexual desire." (See *Alternative Medicine Alert*, June 1999, pp. 64-67.) Their paper lists five progestins in vitex flower and leaf. They conclude, "Vitex may be an option for women who have tried vitamin B_6 and calcium, and who do not wish to use prescription hormonal treatment... Although the effective dose remains unknown, most information suggests using a product that contains 20-40 mg of the dried berry extract standardized to contain 0.5% agnuside. Patients should be aware that results may take up to 18 months."

Recommendation

For women with premenstrual syndrome who are not taking oral contraceptives and are not pregnant or lactating, a several month trial of *Vitex agnus-castus* appears warranted. Recommend it to women who want to try something new and for whom a careful diagnosis has been made. ❖

Hepatitis Associated with Kava Ingestion

Source: Escher M, et al. Hepatitis associated with kava, a herbal remedy for anxiety. *BMJ* 2001;322:139.

"KAVA, THE RHIZOME OF THE PEPPER plant *Piper methysticum*, has been widely used in the South Pacific as a narcotic drink. Lactones, the major constituents of kava, are considered to be pharmacologically active and are sold in Europe and the United States as standardized extracts for anxiety and tension.

"A 50-year-old man presented to his doctor because of jaundice. He had noticed fatigue for a month, a 'tanned' skin, and dark urine.

"The medical history was unremarkable apart from slight anxiety, for which he had been taking three to four capsules of kava extracts daily for two months (maximum recommended dose three capsules) corresponding to a dose of 210-280 mg lactones (Laitain, Schwabe, Switzerland). He took no other drugs and did not consume alcohol.

"Liver function tests showed a 60-fold and 70-fold increase in aspartate aminotransferase and alanine aminotransferase concentrations, respectively. Alkaline phosphatase concentration was 430 IU/l (normal range 30-125), gamma-glutamyltransferase 691 IU/l (9-35), lactate dehydrogenase 1,132 IU/l (125-240), and total and conjugated bilirubin 279.2 micromol/l (6.8-25) and 212.3 micromol/l (1.7-8.6), respectively. Prothrombin time was 25%.

"The patient was admitted to hospital. Ultrasonography showed a slight increase in liver size but no ascites or portal vein thrombosis. Blood tests for hepatitis A, B, C, and E, HIV, cytomegalovirus, and Epstein-Barr virus gave negative results.

"The patient's condition deteriorated within 48 hours. He developed stage IV encephalopathy and had to be intubated. Prothrombin time was then 10%. The patient received a liver transplant two days later. He recovered uneventfully.

"On examination the liver was atrophic, and the subhepatic and portal veins were free. Histology showed extensive and severe hepatocellular necrosis and extensive lobular and portal infiltration of lymphocytes and numerous eosinophils.

"Heavy consumption of kava has been associated with increased concentrations of gamma-glutamyltransferase, suggesting potential hepatotoxicity. A case of recurring necrotizing hepatitis has been reported.

"In our patient a relation between ingestion of kava and fulminant hepatic failure is supported by the chronology, histological findings, and exclusion of other causes of hepatitis. Assessment of causality according to the definitions of the World Health Organization is probable.

Acute liver failure with a fatal outcome or that necessitates liver transplant has been attributed to various herbal preparations. This case illustrates the importance of inquiring about the use of over-the-counter health products. It was reported to the Swiss Pharmacovigilance Center in Berne."

COMMENT

These investigators from Geneva, Switzerland, cite temporal association and exclusion of other etiologies in their linkage of a two-month history of kava ingestion and fulminant hepatic failure requiring transplantation. Only one other case of kava-associated hepatitis has been reported, with rapid reversal of abnormal liver function tests after discontinuation of the herb. The aboriginal communities that use kava heavily have a high carriage rate of hepatitis B surface antigen, a fact thought unrelated to kava use.

Hepatotoxicity is not uncommon with herbals. The authors cite case reports of hepatitis and hepatotoxicity with chaparral (which is on the FDA list of unsafe herbs), Chinese medicine, and an herbal tea. In addition, ginseng, ephedra, shark cartilage, and greater celandine have been associated with reports of hepatitis.

Recommendation

Kava should be avoided in patients with existing hepatic damage, and at elevated risk for hepatic damage and especially alcohol-related injury. Not only are the sedative effects of the alcohol likely to be compounded with concomitant use, but the hepatic damage may as well. ❖

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Complementary and Alternative Medicine for Athletes

Part 1: Ergogenic Aids—Dietary Supplements and Herbal Remedies

By Dónal P. O'Mathúna, PhD

Peer-reviewed by David Schiedermayer, MD, FACP

ATHLETES GO TO GREAT LENGTHS TO PROMOTE THEIR HEALTH. THEY TRAIN HARD, eat carefully balanced meals, rest adequately, seek medical attention for even minor injuries, and purchase expensive gear to minimize injuries. Sometimes, however, they will ingest large amounts of supplements of unknown quality and questionable efficacy in an attempt to enhance their performances. Of the estimated $12 billion in annual sales of dietary supplements, $800 million are for sports supplements.[1] Concerned with athletes' health and fairness in competition, various sporting bodies have stepped into the arena by banning particular substances. Athletes do need to be protected from themselves: In 1997, *Sports Illustrated* asked almost 200 current or aspiring U.S. Olympic athletes if they would take a drug that would make it possible for them to be world champions for five years even though the drug would then kill them.[2] More than half said they'd take it!

Herein lies one of the major concerns with dietary supplements for athletes, and why physicians need a general understanding of the supplements athletes may be using. The pressure to win and perform at one's peak is intensifying among younger athletes. Parents invest thousands of dollars and hundreds of hours in youngsters who compete for traveling teams. On the line is prestige, a college scholarship, a spot in the limelight as an Olympic athlete, or maybe even huge amounts of money as a professional athlete. Given all these payoffs, all this pressure, why not take supplements?

Physicians need to be familiar with the main supplements being used, what evidence supports their effectiveness and safety, and what is known about their impact on adolescents. When athletes come to your office, either for general health issues or problems related to their training or their supplements, it is important to be knowledgeable about the major supplements they may be using. This familiarity will help set the scene for a professional relationship in which athletes are willing to listen to your advice regarding performance-enhancing supplements.

Dietary supplements taken to improve the energy efficiency and performance of athletes are called ergogenic aids. This review will divide these supplements into three main categories: nutritional, steroidal, and herbal ergogenic aids. Most of the nutritional ergogenic aids are found in a well-balanced diet or produced during normal metabolism, but are taken as supplements in the hope they will further enhance performance. Steroids usually are taken to improve the body's ability to develop

INSIDE

muscle mass and recover from intense training so that better performances result. Herbs constitute another diverse group of plant products taken for a variety of ergogenic reasons.

Nutritional Ergogenic Aids

The motivation behind the use of all nutritional ergogenic aids is a desire to get more energy from the fuels consumed in the diet. It is assumed that the athlete is eating a balanced diet, is consuming necessary vitamins and minerals, and is appropriately hydrated and rested. Training and practice take care of the fitness and skill levels needed. Given the athlete's genetic endowment, nutritional ergogenic aids attempt to release more energy to fuel exercise or increase the efficiency of the body's use of that energy.

To understand the reasoning behind the use of many nutritional ergogenic aids, one must understand the basic biochemistry of how cells provide and use energy. The promotional materials used to market these supplements to athletes often include references to related biochemistry. Informed physicians can help athletes and their families understand this information, and spot errors and exaggerated claims. Just because the body's cells use a particular substance, taking it in supplemental form does not necessarily mean the substance will reach those cells. Even if it does get to the cells, it will not necessarily lead to improved performances. Since the body's biochemical reactions are intricately interwoven and counterbalanced, an excess of one metabolite may unbalance other reactions leading to undesirable effects. In addition, there are concerns with the quality of supplements available on the U.S. market, which will be described in detail in the discussion of individual supplements.

The chemical energy compound used by all cells is adenosine triphosphate (ATP). Cells store ATP much like a biochemical battery. And just like regular batteries, they get run down and have to be recharged. Muscles store only enough ATP to fuel exercise for a few seconds. More ATP must then be regenerated using phosphate that comes from creatine phosphate (CP), as shown in Figure 1. Even this adds only enough energy for a few more seconds.[3] This system fuels up to 10 seconds of activity, and is thus most important in short, intense bursts of activity.

After the initial few seconds of exercise, additional energy must be provided by the more familiar metabolic fuels: carbohydrates, fats, and proteins. The first fuel used is glucose, which is released from its storage form, glycogen, contained in both muscle and liver. The glucose is broken down metabolically in the muscle cells after a few seconds of exercise. This process is called glycolysis and results in pyruvate (or pyruvic acid), plus a relatively small amount of ATP. To release the remaining energy from pyruvate, two processes can occur. (*See Figure 2.*)

If athletes are breathing in sufficient oxygen (which requires that they not be exercising too intensely), pyruvate is broken down completely to carbon dioxide, water, and lots of ATP, in a process called aerobic glycolysis. But if the exercise intensifies to where the athlete cannot breath in sufficient oxygen to keep up with energy demands, anaerobic glycolysis kicks in. Some ATP is produced, but only enough to allow intense exercise for 30 seconds to two minutes. After this, the accumulation of lactic acid and accompanying acidosis cause fatigue to set in rapidly. The precise length of time is influenced by training since exercise results in metabolic changes that improve fitness, not just muscular and cardiovascular changes.

Aerobic glycolysis can sustain exercise for a few hours, though only if the intensity is not very demanding. During this time, pyruvate is broken down in the presence of oxygen via reactions called the citric acid cycle (CAC in Figure 2; also known as the Krebs cycle). In addition to producing ATP directly, aerobic glycolysis produces another compound called nicotinamide adenine dinucleotide (NADH). After NADH is processed through another metabolic system called the electron transport chain (ETC in Figure 2), more ATP is produced.

Endurance athletes use aerobic glycolysis to metabolize stored carbohydrates, but stored fat is a more abundant source of fuel. An athlete's body stores much more fat than carbohydrate, and per gram, fat releases almost three times as much energy as carbohydrate. The process by which fat produces ATP is called aerobic lipolysis. Additionally, proteins can be used to generate energy, although they normally provide only 6-7% of the body's energy needs; this can increase to 10-15% if the body's carbohydrate stores are completely depleted.[4]

Phosphates. Given the central role of phosphate as ATP in all biochemical energy systems, increasing phosphate stores in

Alternative Medicine Reports is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/PUBLISHER: Brenda L. Mooney.
EDITORIAL GROUP HEAD: Leslie G. Coplin.
MANAGING EDITOR: Kevin New.
GST Registration Number: R128870672.

Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Alternative Medicine Reports***, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $38 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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United States
$279 per year (Student/Resident rate: $115).
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Outside the United States
$309 per year plus GST (Student/Resident rate: $130 plus GST).

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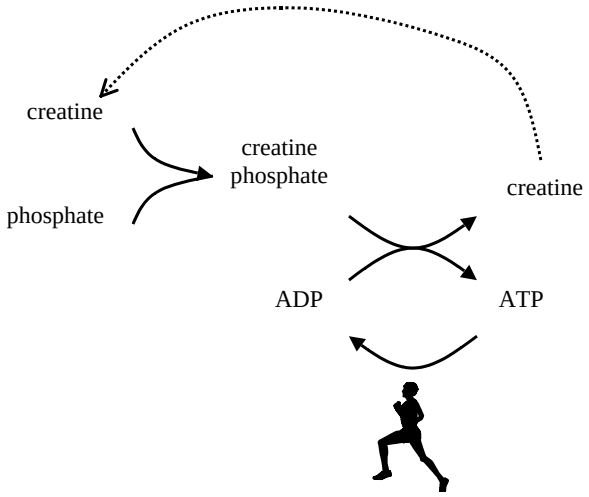
Figure 1

The role of creatine, phosphate, and ATP in exercise



the muscles theoretically might allow the ATP system to function longer and help hasten recovery of depleted ATP stores. (*See Figure 1.*) Phosphate loading is one of the older ergogenic strategies, which usually involves athletes taking 1 g of various phosphate salts three or four times daily for up to a week. Three early studies found that the onset of anaerobic glycolysis was delayed by phosphate loading, but five subsequent studies found no benefit.[5] Variations in the study designs and the formulations used may have led to the inconsistent results.

Currently, the research basis for phosphate loading is unclear but intriguing, given the relatively consistent results among those studies with beneficial findings. However, caution is needed before recommending long-term use of phosphate supplements. Phosphate levels are sensed by the parathyroid glands and thus are linked to serum calcium metabolism. Elevated plasma levels of phosphate lead to secretion of parathyroid hormone, which accelerates kidney excretion of phosphate.[6] Calcium is reabsorbed from bone to facilitate this excretion, leading to concerns about calcium balance in athletes taking phosphate supplements.

Creatine. Creatine is one of the most popular sports supplements, especially among high school football and baseball players. Creatine forms a complex with phosphate (creatine phosphate, CP) that is required to replenish ATP stores in muscles. (*See Figure 1.*) Creatine is essential for short, intense, anaerobic exercise. Its role in exercise has been known since 1847 when the meat of wild foxes was shown to contain 10 times more creatine than that of sedentary foxes raised in captivity.[7] Creatine burst onto the athletic scene in the 1990s when Olympic sprinters admitted they were using it as a legal ergogenic aid. Creatine is not banned by the International Olympic Committee (IOC) or the National Collegiate Athletic Association (NCAA) because it is readily available in meat and fish.

Supplemental creatine theoretically would increase CP stores, thus making more energy immediately available to muscles. Muscles containing additional stored creatine would be expected to replenish depleted CP stores faster, which might hasten an athlete's recovery during repeated bouts of intense exercise. Creatine supplementation usually consists of a loading period of 20 g/d for four to six days (usually taken as 5 g four times a day with food). This is then followed by 2 g/d as a maintenance dose. Others claim the same tissue levels are reached after one month taking 3 g/d as a single dose.

More than 30 randomized, controlled studies have been performed on creatine, though none with more than 40 subjects. A meta-analysis of 32 studies presented at the American College of Sports Medicine 2000 meeting showed no overall effect of creatine supplementation on anaerobic performance.[8] However, some patterns are visible when the studies are subgrouped into similar categories.[9] Oral creatine supplementation does not appear to improve single-bout anaerobic exercise, submaximal exercise, or aerobic exercise. Improvements here would not be expected since the ATP-CP system is not highly significant with these types of exercise.

However, some improvements generally have been seen with repeated bouts of maximal exertion lasting 6-30 seconds with a few minutes recovery. This type of exercise would be expected to be strongly dependent on CP. Many football plays, hitting and running the bases in baseball, and playing soccer depend heavily on the CP system. Four studies published in 2000 found positive effects for creatine supplementation accompanying interval training for cyclists, soccer players, and weight lifters.[8] In this type of training, athletes do intense, short-duration exercises, followed by a recovery period (the interval), and then repeat the cycle. None of these studies examined if athletes' competitive performances improved, although creatine supplementation appeared to allow them to train more vigorously. Great variability also has been noted in the responses of different athletes to the supplements.

Creatine supplementation appears to provide benefit for specific types of intense, short-duration exercise. Benefits for endurance, single-burst, and recreational exercise have not been demonstrated. Although few adverse effects have been reported, there is some concern that creatine may cause kidney problems in those already predisposed to kidney disease. One study has followed a group of athletes using creatine for up to five years.[10] Nine athletes, who used between 1 and 80 g/d creatine, were compared to 85 physical education and physical therapy students who were not taking creatine supplements. No significant differences were found in plasma or urine levels of creatinine, urea, or albumen. Plasma creatine levels were not significantly different, but urinary creatine levels were almost 38 times higher, on average, among those taking the supplements. The authors concluded that creatine supplementation has no detrimental effects on the kidneys.

Anecdotally, creatine supplementation is reported to lead to muscle cramping and water retention, but these adverse effects not been confirmed in studies. In January 2001, the Food Safety Agency in France (www.afssa.fr) called for creatine to be listed as a banned substance because of its potential to cause

cancer and other tissue damage, especially when taken long-term. There is no information on its impact on adolescents. The American College of Sports Medicine recommends against creatine supplementation for those under 18 years.[11]

Pyruvate. Pyruvate is a three-carbon molecule made when glucose is split in two by metabolism. (*See Figure 2.*) Pyruvate developed a reputation as a "fat burner" based on two studies by Stanko, which have not been replicated.[12] Stanko used a combination of 25 g pyruvate with 75 g dihydroxyacetone (DHA), a metabolite produced immediately before pyruvate during glycolysis. Four other studies by Stanko found that obese women confined to metabolic wards lost more weight and more fat when taking pyruvate and DHA than those taking placebo. However, the applicability of these results to athletes is questionable.

The mechanism by which pyruvate might be ergogenic is unknown. Some have speculated that pyruvate may enter a "futile cycle" where a reaction proceeds forward and backward, continuously expending energy.[13] This may benefit those seeking to lose weight, but not athletes. Since pyruvate is a natural substrate for aerobic and anaerobic glycolysis, theoretically it would provide calories just like other carbohydrates.

While pyruvate as an ergogenic aid is said to be research-supported, the two published studies were conducted with untrained men. Stanko himself recommends that athletes take 2 g/d pyruvate, but this differs completely from the dosage used in his trials. Commercial preparations also use a different proportion of DHA, or none at all. Between one-third and one-half of the research participants had diarrhea and borborygmus, which would be counterproductive in athletes. Long-term effects of supplementation have not been examined. Until Stanko's results are replicated with athletes, use of pyruvate is unwarranted.

Chromium. Chromium is more popularly used in weight-loss products, but also is alleged to be an ergogenic aid. Chromium is an essential trace element involved in the normal functioning of insulin.[14] The Adequate Intake Level for chromium set by the Institute of Medicine (IOM) in 2001 was 35 mcg/d for young men and 25 mcg/d for young women.[15] However, little detriment has been found in those consuming 15-25 mcg/d. Such small amounts are difficult to measure accurately, which has hampered clinical research with chromium.

Chromium supplementation has been demonstrated to improve diabetes symptoms for those who also are chromium deficient. Results have been variable with diabetics having normal chromium intakes. Insulin facilitates metabolism of glucose and fatty acids, and transport of amino acids into muscle. On this basis, chromium has been touted as a fat burner and muscle builder. Four studies of athletes given 200 mcg/d of chromium showed no increase in muscle mass or decrease in body mass.[14] This matches the general lack of efficacy found with studies of chromium for weight loss.[16]

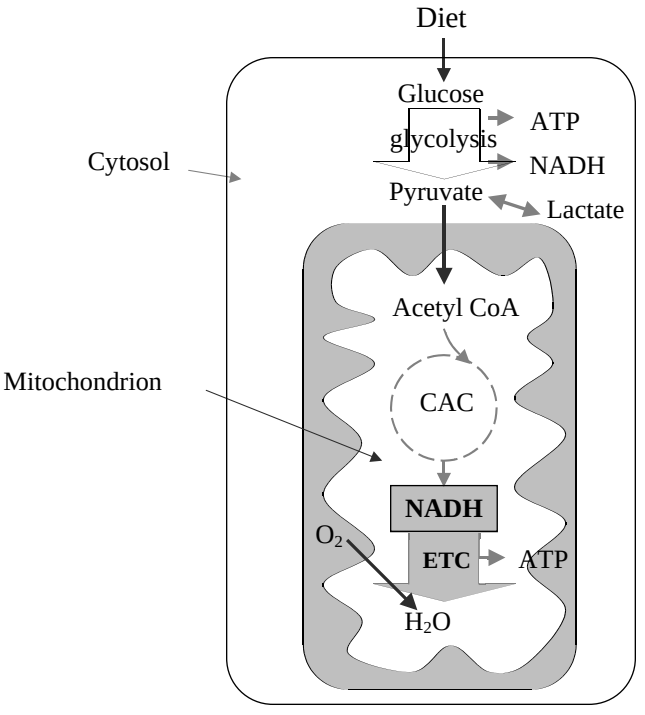
No adverse reactions were reported in any of the clinical studies with chromium supplements, and the IOM report found insufficient evidence to set a Tolerable Upper Intake Level. Animals given large daily doses of chromium showed no adverse effects, although two in vitro tests found evidence of chromosomal damage. Some have raised concerns with the particular formulation of the mineral as chromium picolinate, which increases its absorption but also may make adverse effects more likely. A small number of case reports of adverse effects exist, while the U.S. Food and Drug Administration (FDA) has received more than 500 adverse event reports involving chromium as part of multi-ingredient herbal remedies.[17] Overall, the efficacy of chromium as an ergogenic aid is questionable.

Carnitine. Turning from ergogenic aids used to impact glycolysis, carnitine is used to improve fatty acid metabolism. Carnitine is an amino acid, although different from those found in proteins. Once thought to be a vitamin, it is now regarded as non-essential because sufficient quantities are made endogenously from dietary amino acids. Fatty acids must be transported into the mitochondria of muscle cells before being metabolized to release their energy. This process requires carnitine. Theoretically, carnitine supplementation might allow athletes to utilize fatty acids better, spare glycogen stores, and thus lead to improved performances in endurance events.

Carnitine supplementation studies have failed to demonstrate regularly that oral ingestion of carnitine leads to increased muscle carnitine levels.[5] Some studies have shown that fatty acid metabolism improved and glycogen stores

Figure 2

Energy production in a cell



were spared, but an equal number have demonstrated no benefit.[18] Those studies that examined exercise performance demonstrated no benefits from carnitine supplementation.

Carnitine usually is recommended in doses of 2 g/d. Few side effects have been noted at this dose, although some people experience diarrhea. The long-term effects of taking carnitine have not been tested, either for safety or efficacy in endurance athletes. Carnitine is available in two isomeric forms: D-carnitine and L-carnitine. The form found in nature is L-carnitine and this is the only form that should be used. D-carnitine may interfere with endogenous synthesis of L-carnitine, leading to its deficiency, which can result in muscle weakness and dysfunction.

Coenzyme Q_{10}. Coenzyme Q_{10} (also called CoQ_{10} or ubiquinone) is another nutrient found in mitochondria. It plays a vital role in the electron transport chain (ETC), which directly involves oxygen in the release of energy from nutrients. For this reason, CoQ_{10} supplementation has been recommended for endurance athletes as a way to maximize aerobic metabolism. Early reports of six studies appeared to support this finding, in addition to numerous other reports of the benefit of CoQ_{10} in treating heart disease.[18] However, these early reports were from conference proceedings that have not been published.

More recent controlled studies published in peer-reviewed journals showed no benefits from CoQ_{10} supplementation in triathletes, marathoners, cyclists, and untrained men.[19] CoQ_{10} is an antioxidant, which is why some believe it is beneficial in preventing heart disease. A recent study of CoQ_{10} given along with other antioxidants showed no ergogenic effect.[20]

No adverse effects were reported after taking 70-150 mg/d CoQ_{10} for several weeks. However, one study reported evidence of muscle damage after intense exercise in athletes who took 120 mg/d CoQ_{10} for 20 days.[21] Given that there is no evidence that CoQ_{10} supplements are effective ergogenic aids, any risk would speak against their use by athletes.

Glutamine. Glutamine is a nonessential amino acid, although some authorities have reclassified it as "conditionally essential." This means that under certain circumstances the body is unable to make sufficient glutamine endogenously and supplementation may be required. Glutamine plasma levels are lower during catabolic conditions, such as those following surgery, trauma, sepsis, burns, and extended, high-intensity exercise.[22] The body's largest stores of glutamine are in skeletal muscle, which can be broken down to replenish plasma glutamine levels. Protein breakdown and tissue wasting also can occur because of elevated cortisol levels, which can arise as a result of prolonged physical stress.

Supplemental glutamine is thus advocated as an anticatabolic agent to counteract cortisol and replenish plasma glutamine levels. Hospital patients with major physiological stress sometimes are given glutamine supplements. Glutamine is an important energy source (along with glucose) for many cells in the immune system, including lymphocytes and macrophages. Several studies have demonstrated that athletes have higher incidences of upper respiratory tract infections (URIs) following prolonged, endurance exercise. For example, 13% of athletes who completed the Los Angeles marathon had infectious illnesses the week after the race compared to 2.2% of athletes with similar training regimens who did not compete that day.[23] Runners who train more than 60 miles per week have a higher risk of infection, as do dancers and military personnel after intensive training.[24]

Athletes use glutamine supplementation to counteract both cortisol production and immunosuppression following exercise. Clinical studies have focused on glutamine's effect on the immune system, with results in athletes being contradictory. The results of eight small studies were combined and showed that athletes had fewer URIs in the week following a marathon or ultra-marathon if they consumed glutamine immediately after the race.[25] The incidence of URIs in athletes who drank 5 g glutamine in two portions after the race was 19.2%, compared to 51.2 % among those who drank a placebo drink.

However, a number of other studies with marathoners, swimmers, and cyclists found lower plasma glutamine levels after prolonged exercise, but unchanged immune cell counts.[12] Correlations between physiological measurements and incidences of URIs were not found in the study with swimmers. Overall, there is little clinical evidence to support the use of glutamine supplements except immediately after an intense endurance event to reduce the chances of developing a URI in the following week. Glutamine is safe and not known to interact with other drugs or supplements.

HMB. Beta-hydroxy-beta-methylbutyrate (HMB) is a normal breakdown product of the essential branched-chain amino acid, leucine. HMB also occurs naturally in high levels in catfish and citrus fruits.[12] Animals given HMB demonstrated less protein breakdown and a slight increase in protein synthesis. Athletes, therefore, take HMB hoping it will reduce protein wasting during periods of high stress and exercise. Two studies have shown evidence to support these claims, although overall the results remain preliminary.

Forty-one untrained men on a high-protein diet were randomly assigned to receive either 0, 1.5, or 3.0 g/d of HMB.[26] After lifting weights for 90 minutes, three days a week for three weeks, the men taking HMB had 20-60% lower levels of biochemical markers that indicate protein breakdown. Muscular strength increased 8% for those in the placebo group, 13% for those taking 1.5 g HMB, and 18.4% for those taking 3.0 g HMB. In the second study, 28 athletes took either 0 or 3.0 g HMB and lifted weights for two to three hours, six days a week for seven weeks. At two, four, and six weeks, the supplemented group had a significantly greater increase in fat-free body mass than the placebo group. However, the difference between the groups peaked between weeks two and three, and was no longer statistically significant at week seven. The HMB supplemented group increased in bench press strength compared to the placebo group, but not with the squat lift or hang clean.

These results suggest that HMB may be effective as an ergogenic aid, but the second study suggests the benefits may be short-lasting. Until these studies are replicated, enthusiasm

for HMB should be restrained. The safety of taking HMB for extended periods of time also must be investigated.

Steroidal Ergogenic Aids

Testosterone, the chief male hormone, has both anabolic effects that increase muscle mass and strength and androgenic effects that lead to masculinization. Synthetic steroids of interest to athletes attempt to maximize the anabolic effects while minimizing the androgenic effects. Some of the more commonly used anabolic agents include nandrolone, stanozolol, oxandrolone, and oxymetholone.[6] These agents are banned by most sporting organizations, yet their use remains high in certain sports. The 1990 Anabolic Steroids Control Act made it more difficult to obtain these without prescription, but a black market thrives on the drugs, often sold for 10 times their retail cost.

Considerable debate has occurred over the years regarding whether anabolic steroids improve athletic performance and what risks they might carry. Some clinical research suggests anabolic steroids do not increase muscle mass or strength, yet many athletes anecdotally report significant gains. One reason for this discrepancy may have to do with the way steroids are used by athletes. Athletes usually combine steroid use with high-intensity training and protein-rich diets. Many different steroids are taken in complicated regimens that allegedly maximize the anabolic effects and minimize the risks of both adverse effects and getting caught. Athletes usually will give themselves 10-100 times the doses clinical researchers would recommend. On top of this, athletes often take other supplements and herbal remedies reputed to stimulate the body's production of endogenous anabolic steroids. These differences may account for discrepancies between the reputation of anabolic agents in the gym and the medical literature. However, more recent research with higher doses of anabolic agents do demonstrate an ergogenic effect.[27] Coupled with this are recent revelations concerning the systematic use of anabolic steroids in the former East Germany, especially by female athletes, which led to their dominance in many events during the 1970s and 1980s.[28]

Anabolic steroids have been implicated in causing serious adverse effects.[6] Exogenous steroids will suppress the body's own production of testosterone. This effect can continue for months after the anabolic agents are discontinued, and some cases of sterility have been reported. In addition, gynecomastia, prostate problems, connective tissue damage, and increased blood platelet aggregation have been reported. Anabolic agents are metabolized by the liver, leading to concerns about liver damage after long-term use. Oral anabolics in particular lower HDL cholesterol levels and elevate LDL and total cholesterol levels, which could put the athlete at higher risk for coronary heart disease. Women who take anabolic steroids are also at higher risk for virilization, masculinization, altered menstrual function, hirsutism, decreased breast size, and enlarged clitoris. Taking steroids may lead to premature closure of bone plates in adolescent boys and girls, thus disrupting their normal growth patterns.

Given the wide range of serious and life-threatening side effects, and widely accepted principles of sports ethics, most sporting organizations ban the use of anabolic agents by athletes. Yet a few physicians and pharmaceutical researchers continue to produce and prescribe agents to keep athletes one step ahead of those enforcing these bans. At the same time, some athletes turn to legal sources of steroids—prohormones. These naturally occurring compounds are sold as dietary supplements in the United States without restriction. Yet there is even less information available on their effectiveness, and just as much concern about their safety, especially in adolescents.

The use of various supplements is usually justified by their role in the synthesis of testosterone. However, Figure 3 shows that these biosynthetic pathways are interwoven and balanced in complicated ways. Adding one exogenous component to this web of steroids influences many of the others, often in unpredictable ways.

Androstenedione. The steroid androstenedione (or "andro") occurs naturally in Mexican wild yams and Scotch pine, and thus can be sold practically unregulated as a dietary supplement in the United States under the 1994 Dietary Supplement Health and Education Act (DSHEA). Humans produce andro naturally in the adrenal glands and gonads and it then can be converted into testosterone, estrone, estradiol, androsterone, and other steroids. (*See Figure 3.*) Androstenedione's direct anabolic-androgenic activity is weak.

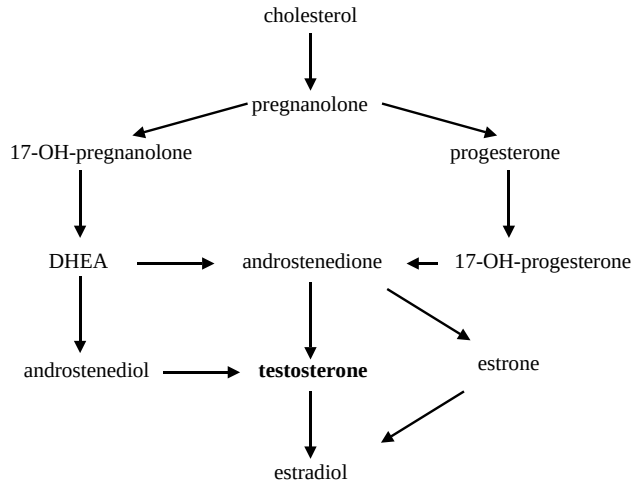
Andro was first developed as an anabolic agent in East Germany in the 1970s. It was used as a nasal spray, allegedly producing higher serum testosterone levels that were short lasting to avoid detection at competitions. It appeared on the U.S. athletic scene in 1996, and received much publicity when Mark McGuire announced he was using it during his successful bid to break Roger Maris' home run record.[29] A year later, after much controversy surrounding his example to young athletes, McGuire announced he no longer used andro.

The first controlled study on andro as an ergogenic aid was published in 1999.[30] In the first part, 10 healthy men were randomly assigned to receive either 100 mg androstenedione or placebo. Those taking andro had significantly elevated blood androstenedione levels for 4.5 hours, which had dropped again within six hours of taking the dose. Other serum hormone and testosterone levels remained unchanged.

In the second part of the study, 20 healthy men were randomly assigned to androstenedione (100 mg tid for two weeks, followed by a week off to simulate the practice of "washing out" used by athletes) or placebo. The cycle was repeated three times. All subjects were supervised lifting weights for all major muscles three times weekly on nonconsecutive days. Body composition, muscle strength, and muscle fiber analysis changed for all subjects as would be expected with a weight-training program. The two groups showed no significant differences in these changes or in their blood testosterone levels. The only differences in their blood analyses were that those taking andro had significantly higher estradiol, estrone, and estrogen levels, and 12% lower HDL cholesterol levels. These changes raised concerns about the negative effects of long-term andro use in causing cancer and heart disease.

Figure 3

Androgenic human steroids



Another double-blind study randomly assigned 40 middle-aged, trained men to one of three groups.[31] Each person consumed one 50 mg capsule of either placebo, androstenedione, or DHEA (dehydroepiandrosterone) bid. After 12 weeks, there were no significant differences between the three groups in lean body mass, strength, or testosterone levels. No adverse effects were reported.

Two more andro studies were published in 2000. The first involved 10 men who had lifted weights for several years and never used anabolic steroids. They were randomly assigned to take either 200 mg androstenedione or placebo for two days and then perform a heavy resistance-training program.[32] Blood samples were drawn for 24 hours starting the morning of the second dose. Two weeks later the men repeated the protocol, except they ingested the other material in this double-blind, crossover study.

Blood plasma levels of androstenedione were two to three times higher than baseline after consumption of the supplement, but unchanged after the placebo. However, total testosterone and free testosterone levels were unchanged in both groups. After 90 minutes of weight lifting, total and free testosterone levels were transiently elevated in both groups, but the difference was not statistically significant. Those taking andro showed significantly elevated estradiol levels compared to placebo.

The second andro study conducted in 2000 randomly assigned 50 men to receive either placebo, androstenedione (100 mg bid), or androstenediol (100 mg bid).[33] Androstenediol is closely related to androstenedione. (*See Figure 3.*) For 12 weeks, the subjects exercised three times a week under the supervision of a personal trainer who recorded all exercises completed. After four weeks, the androstenedione group had significantly elevated free and total testosterone levels compared to androstenediol and placebo. However, by the end of the study there were no differences. Both andro supplements led to significantly elevated levels of estradiol and estrone, which remained elevated until the end of the study. No significant differences were found between the three groups in body composition or muscle strength tests.

All controlled studies have shown similar results. Andro supplementation increases the plasma levels of androstenedione, which leads to increased production of female estrogen hormones, but not testosterone. When testosterone levels did increase, they were always short-lived. Supplementation produced no body composition or muscle strength improvements. Therefore, androstenedione appears to have none of the advantages athletes seek, and all of the dangers inherent to anabolic steroid abuse.

The four studies reported thus far have all involved men. The early German work with androstenedione involved female athletes. Also, a 1966 study with radioactive tracers found that androstenedione leads to only 0.3% of the testosterone produced in males, but to about 60% of that produced in females.[32] It thus appears theoretically unlikely that men will experience any anabolic benefit from androstenedione supplements, although the effects in women have not been examined in controlled studies.

Androstenedione and androstenediol are banned by many sports organizations, including the IOC and NCAA.[34,35] Consuming these products will, in most cases, lead to a positive urine test for nandrolone, another banned anabolic agent.[1] The quality of andro products available in the United States also is problematic. Of nine products tested in one study, six failed the commonly accepted USP standards of containing between 90% and 110% of labeled quantities.[1] One contained no androstenedione at all, and one contained 10 mg testosterone without revealing this on its label.

DHEA. DHEA is another testosterone precursor that has been used as an ergogenic aid. DHEA also is present in the blood as its sulfate ester (DHEAS) and together these constitute the most abundant steroid in humans. However, both forms have weak steroidal actions and appear to act primarily as precursors for other steroids. (*See Figure 3.*) Much remains unknown about DHEA's effects in the body, although its level peaks when people are in their 20s, and then gradually decreases as a person ages. For this reason, some have claimed that DHEA supplementation is the fountain of youth and the answer to all health problems. Prior to 1994, DHEA was an unapproved drug available only by prescription, but DSHEA reclassified it as a dietary supplement. Sales immediately soared, and athletes began taking it as if it were an anabolic steroid. The IOC and NCAA banned its use.[34,35]

Much of the research claiming to support DHEA's effectiveness has been conducted on animals. Of relevance to athletes, these studies have found that DHEA can increase muscle mass, reduce fat mass, improve insulin sensitivity, and even extend life span.[6] However, the relevance of these studies for humans is questionable since only humans and a few primates synthesize and secrete DHEA and DHEAS.[36]

In human research, a few small studies have found some benefits when older men and women take DHEA supplements (usually 100 mg/d). Supplementation returned blood DHEA levels to their youthful levels, with women (but not men) also

having some increase in androstenedione and testosterone levels. In one study, older men (but not older women) reported increases in knee and lumbar back strength.[36]

The first clinical trial of DHEA had two parts.[37] In the first, 10 healthy, untrained men took 50 mg DHEA which led to significantly elevated blood androstenedione levels within 60 minutes, but testosterone and estrogen levels remained unchanged. In the second part, 19 healthy men were randomly assigned to DHEA (150 mg/d) or placebo. DHEA was taken for two weeks, followed by a week off to simulate washing out, and the cycle was repeated three times. All subjects were supervised lifting weights for all major muscles three times weekly on nonconsecutive days. The two groups showed no significant differences in serum testosterone, estrogen, or lipid levels. Both groups changed in strength and lean body mass as would be expected after a resistance-training program, with no statistical differences between the two groups. The only other clinical trial of DHEA for sports performance also examined androstenedione and was described in the andro section.[31] No beneficial effects from DHEA supplementation were found.

DHEA use has adverse effects, being associated with acne, increased facial hair, loss of scalp hair, deepening of the voice, weight gain, decreased HDL cholesterol, abnormal liver tests, insulin resistance, and mild insomnia.[6] The quality of commercial products available also has been found to be problematic. One study found that products contained between 0% and 150% of the labeled DHEA amount, with nine of the 16 products failing to meet standard pharmaceutical specifications of 90-110% of labeled amount.[38] There is little reason to support the use of DHEA by athletes, and many reasons to discourage its use.

Human Growth Hormone. Although human growth hormone (hGH) is not a steroid, it is included in this section because athletes use it in the hope of obtaining an anabolic effect. A polypeptide secreted from the pituitary gland, hGH affects all body tissues. It stimulates growth of bone and cartilage and is especially important during childhood for normal development of body size. Children with a genetic deficiency in the hormone's production are substantially shorter than average if not treated with hGH replacement therapy. Human growth hormone also enhances oxidation of fatty acids and reduces the breakdown of glucose and amino acids, which contribute to its reputation as an ergogenic aid.

Resistance training has been shown to increase secretion of hGH, leading to speculation that the growth of muscle mass seen with resistance training is mediated, at least in part, through hGH. Injections of hGH became popular among power athletes in the early 1990s. This became so prevalent that some dubbed the 1996 Olympic Games in Atlanta "the Growth Hormone Games."

Most of the data on injected hGH supplements are based on studies conducted in men 60 years or older. These men showed improvements in muscle tone, increased lean body mass, and reduced fat mass.[39] However, in younger trained or untrained adults undergoing resistance training, well-controlled clinical trials showed that hGH supplementation did not increase muscle synthesis, muscle size, or muscle strength.[18] There are significant concerns about hGH injections for those who are not deficient in the hormone. Insulin resistance has developed, along with fluid retention, gynecomastia, and headaches.[39]

Because of these concerns, hGH preparations are now available for oral administration, especially as a sublingual spray. There is no evidence that oral hGH has any effect on the body. Another recommendation has been to supplement the diet with arginine, ornithine, and lysine—amino acids believed to stimulate the secretion of hGH. A 1989 study found beneficial changes in fat and muscle mass after five weeks of supplementation with these amino acids, but later, better-designed studies have failed to replicate these findings.[18] Moderate doses of these amino acids appear to be safe, but excessive intake can lead to gastrointestinal problems. Long-term, high-level supplementation may precipitate kidney or liver problems in susceptible individuals.

Herbal Ergogenic Aids

Ginseng. One of the most popular herbal remedies sold in the United States, ginseng has a reputation as an adaptogen: a substance that helps the body adapt to stressful situations.[40] Given the stress of training and competition, ginseng's popularity has extended into sports circles. In fact, ginseng is one of the few herbal remedies that has been investigated extensively by sports medicine researchers.

Ginseng demonstrates the problems inherent with the use of any herbal remedy in the United States today. The term ginseng applies to many different plant species. The ginseng used for centuries as part of traditional Chinese medicine (TCM) is Asian ginseng, or *Panax ginseng*. American ginseng is a closely related plant (*Panax quinquefolius*), but Siberian ginseng (*Eleutherococcus senticosus*) is only distantly related to either. Several other species have been used and sold as ginseng, but the available research for sports performance has focused primarily on Asian and Siberian ginseng.

The active ingredients in Asian and American ginseng are believed to be a group of at least 30 steroidal glycosides called ginsenosides. However, particular batches of each species contain different mixtures and amounts of ginsenosides, which may account for the different results found in clinical trials. Siberian ginseng contains no ginsenosides, but a different group of steroidal glycosides called eleutherocides. Traditionally, Asian ginseng is harvested after at least five years of growth, at which time the roots typically contain 1-2% ginsenosides.[40] TCM practitioners generally recommend 3-9 g/d ginseng, usually combined with other herbs. With the availability of standardized preparations, 200 mg/d ginsenosides is the usual recommendation.

However, the plant material can vary greatly. The levels of ginsenosides 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 m^2 area, the ginsenoside content varied more than twofold.[41] Not only does the ginsenoside content of species and plants vary, but the plant material can be processed in very different ways. The most

common form is "white ginseng," which is the bleached and dried root material. "Red ginseng" is steam-cured prior to drying, which leaves a reddish color in the product. Other teas, extracts, and tinctures (alcohol-based extracts) also are available. All of these options have led to great variability in ginseng products available to athletes today.

Clinical trials on ginseng for sports performance date to the early 1970s. However, the quality of the early studies often was poor; several of them were not controlled in any way. A 1994 review of this research concluded, "there is an absence of compelling research evidence demonstrating the ability of ginseng to consistently enhance physical performance in humans."[42] However, animal studies have found that ginseng and ginsenosides consistently help animals adapt to physical and chemical stress. Those studies have tended to use much higher doses (up to 100 times higher) than those given to humans.

When these same reviewers updated their analysis in 2000, they found more than 35 new reports on ginseng related to physical performance.[43] While the methodological quality of these trials had improved, many still had significant problems, especially with sample size. In studies measuring physiological parameters, the largest sample size was 43, and all but three studies had fewer than 20 subjects. The doses, species, and preparations of ginseng given to athletes also varied significantly, as did the lengths of the studies.

Eight controlled clinical trials of Asian ginseng for physical performance in humans were published during the 1990s.[40,43,44] Of these, six produced nonsignificant results in a variety of physiological measurements. One crossover study found no benefit during the first period of supplementation, but in the second period found that athletes lost physical fitness slower when taking 400 mg/d ginseng.[45] The authors cautioned that this could have been a carryover effect from the first period. The second study with beneficial effects found improved measures of fitness in those who took ginseng and did not exercise compared to those who took a placebo without exercising.[46] Ginseng provided no benefit to those who exercised. One controlled study used American ginseng and found no significant improvements. Since 1990, two controlled trials have used Siberian ginseng, with both having nonsignificant results. Overall, nonsignificant results predominate in the later, better-designed studies of ginseng for athletic performance.

Adverse effects of ginseng have been reported occasionally, although most have been relatively minor and short-lasting.[44] A "ginseng-abuse syndrome" also has been alleged when people consume 3 g/d ginseng, and especially with 15 g/d. The symptoms of the latter are hypertension, nervousness, sleeplessness, and diarrhea.[44] The quality of products available in the United States also has been of concern. In one analysis, only nine of 22 ginseng products passed a quality control test, with eight products found to contain higher than allowed pesticide levels.[47] Although ginseng is not banned by the IOC or NCAA, one athlete at the 1988 Seoul Olympics tested positive for the banned substance ephedrine, which was traced to contamination of a ginseng product.[48] This is alleged to be a consistent problem with ginseng supplements.

In spite of a relatively large number of clinical trials, ginseng has not produced the dramatic improvements commonly heard in anecdotal reports. While it is possible that the research protocols have not matched the way ginseng is used by athletes, studies consistently find ginseng has little direct impact on athletic performance. However, there is growing evidence that ginseng may offer psychological benefits that could be relevant for athletes, especially if the athletes feel more confident before competition.[49] Further study is needed in this area, but it may explain the large discrepancies between research findings and the long tradition of ginseng usage. Overall, there is little research support for the use of ginseng as an ergogenic aid.

Ephedra. Ephedra also is known by its Chinese name of ma huang, as "herbal ecstasy" for its stimulant effect, and as "herbal fen-phen" for its alleged weight-loss properties. The plant material traditionally used is the rhizome and roots of Chinese ephedra (*Ephedra sinica*). The herb has a long tradition of use in China for several respiratory problems. The active ingredients are a group of compounds called ephedrine alkaloids. The best known of these is ephedrine, the widely used decongestant and asthma remedy. The genus *Ephedra* contains more than 40 different plant species, each with its own specific alkaloid mixture. *Ephedra nevadensis*, often called American ephedra or Mormon tea, is native to North America, but contains no ephedrine alkaloids.

The total alkaloid content of Chinese ephedra ranges from 0.4 to 25 mg/g of plant material.[50] This variability has extended into the commercial products available as dietary supplements. Several hundred adverse event reports, including about 50 fatalities, have been reported to the FDA after people took ephedra products. For this reason, the FDA requires that ephedra product labels state that no more than 8 mg ephedrine alkaloids should be taken every six hours for a total of no more than 24 mg/d and that treatment should be stopped after seven days.[12] However, one study found between 0.3 and 55.6 mg ephedrine alkaloids per gram of ephedra product.[51] Another study found a 19-fold difference in the amounts of ephedrine alkaloids in 10 commercial products.[50] These studies also found that some products contained ephedrine without any other ephedrine alkaloids. Since no *Ephedra* species produces only ephedrine, the most reasonable interpretation of these results is that the products were spiked with synthetic ephedrine. The variability among products could lead to people taking vastly different quantities of ephedrine, especially if they change from one brand to another.

All ephedrine alkaloids work in similar ways to epinephrine (adrenaline) as sympathomimetic agents. They stimulate numerous systems in the body, leading to faster heart rate, increased blood pressure, flushing, deeper breathing, and nervousness.[52] For this reason, ephedrine and related products are banned by most sporting organizations, including the IOC and the NCAA.[34,35] Ephedrine alkaloids can cause insomnia, which can be both a desired effect or an unwanted side effect. The cardiac and neurological adverse effects are more serious.

In spite of ephedrine's stimulant effects, there is little

evidence it promotes athletic performance. Five controlled clinical trials giving athletes up to 120 mg ephedrine alkaloids found no significant performance enhancement effects.[40] However, combination of ephedrine (1 mg/kg) with caffeine (5 mg/kg) significantly increased time to exhaustion compared to either drug alone or placebo.[53] Combined ephedrine-caffeine products also are alleged to promote weight loss, though there is little evidence to support this practice. The combination allegedly causes fat loss preferentially while increasing muscle mass.

Overall, the evidence for athletes using ephedrine alkaloids clearly points to the dangers far outweighing any benefits. Athletes should be discouraged from taking any ephedra or ma huang product. Part of the concern here arises from the poor quality of ephedra products found in several studies. In addition, ephedrine is banned by many sporting organizations, and ephedra herbal products will lead to positive drug tests.[40]

Caffeine. Caffeine is a unique compound in the sports world in that it is part of the diet of most athletes, has no nutritional value, and is banned by the IOC only if its level exceeds 12 mcg/mL of urine.[54] The maximum urinary level allowed by the NCAA is 15 mcg/mL.[35] While caffeine commonly is found in coffee, tea, cocoa, chocolate, and many soft drinks, herbal sources include kola nut, guarana paste, and maté leaves. These frequently are added to combination herbal remedies for their caffeine content. However, most of the studies have been conducted with synthetic caffeine that allows precise and reproducible dosing. Herbal caffeine sources have all the variability problems discussed of ginseng and ephedra products.

Since 1990, research has found consistent evidence that caffeine supplementation does have an ergogenic effect. Caffeine may stimulate the sympathetic nervous system and thus augment the effects of ephedrine.[5] Other metabolic studies suggest caffeine may lead to the release of free fatty acids and enhance their oxidation. This could lead to a glycogen sparing effect, which might improve endurance performance.

Several controlled studies have found that both well-trained and recreational athletes improved their endurance performances by 20-50% after ingesting around 300 mg caffeine.[54] These improvements increased with increasing doses of caffeine. In one study, caffeine (3, 5, and 6 mg/kg) produced ergogenic effects without side effects and without exceeding the IOC urinary output limit.[55] Higher doses (9-13 mg/kg) produced greater ergogenic effects, but prevalent side effects (dizziness, headache, insomnia, and GI disturbances), and with several athletes exceeding the IOC urinary limit.

Results with caffeine supplementation prior to sprinting or intense exercise lasting less than 20 minutes have been contradictory. Ergogenic effects in these studies have been explained on the basis of caffeine's central stimulant effects, which are believed to increase athletes' alertness and improve mood.[54] Researchers do not have a clear understanding of all the mechanisms by which caffeine affects performance.

Caffeine remains a controversial, though tolerated, ergogenic aid. Research demonstrates that it can improve endurance performance, although individual responses vary considerably. Caffeine raises ethical questions concerning how "natural" an athlete's performance should be. Endurance athletes who consume six 8-oz cups of coffee in the hour prior to exercise will approach the IOC limit of 12 mcg/mL urinary caffeine. Capsules, tablets, and suppositories regularly are used by athletes seeking the ergogenic effects. A study of 11- to 18-year-olds in Canada found that 26% of the athletes used caffeine to enhance performance.[5] Athletes taking more than 9 mg/kg sometimes reported poorer performance because of caffeine's side effects. Some have expressed concern that caffeine's diuretic effects may lead to dehydration, but this has not been found in research studies.[54]

Cordyceps. Cordyceps is another example of an ancient Chinese herbal remedy gaining a reputation as an ergogenic aid. The remedy comes from the fungus *Cordyceps sinensis*, which grows in the Himalayan mountains. Previously unknown female Chinese distance runners and swimmers came to international prominence in the mid-1990s and attributed their success to rigorous training and a special diet including cordyceps.[56]

Cordyceps extracts contain numerous compounds, many of which could contribute to an ergogenic effect.[57,58] They contain relatively large amounts of adenosine, which is a vital constituent of ATP, the high-energy molecule fueling many cellular processes. (*See Figure 1.*) Cordyceps extracts are plentiful in the essential amino acid, tryptophan (24 mg/g), which can have a calming effect on humans and thus could contribute to improved performances. A number of tissue studies have shown that cordyceps extracts cause bronchodilation, which validates its traditional Chinese use.[59] However, no clinical trials have examined the alleged ergogenic effects of cordyceps.

Harvested cordyceps is extremely expensive, but fermentation technology has made it more available to athletes and researchers. Research is starting to support the theoretical basis of an ergogenic effect, but this has not been examined in human trials. One commercial product, CordyMax™, contains 525 mg of a dried extract standardized to contain at least 0.14% adenosine. The manufacturer recommends taking two capsules, two or three times daily. However, reports of contamination of imported Chinese remedies regularly occur, and cordyceps is no exception. Two cases of lead poisoning were reported in Taiwan after people ingested cordyceps powder, later found to contain 20,000 ppm lead.[60]

Plant steroids. Wild yam (or Mexican yams, *Dioscorea villosa*) is the most popular herbal remedy known to contain plant steroids. Others include saw palmetto (*Serenoa repens*), wild oats (*Avena sativa*), potency wood (*Ptychopetalum olacoides*), smilax (*Smilax officinalis*), suma (*Pfaffia paniculata*), and sarsaparilla (*Smilax* species).[40] Rice bran oil also has been used as a source of gamma-oryzanol. All are used as "legal" sources of testosterone or prohormones.

However, in spite of the popularity of this approach to getting a "testosterone boost," there is no evidence that it works.

One double-blind, randomized clinical trial with 20 young men examined a herbal remedy containing six prohormones, including 300 mg androstenedione, 150 mg DHEA, and 540 mg saw palmetto.[61] Subjects took the supplement for two weeks and then took a week off, and repeated the protocol three times. They lifted weights three days a week for eight weeks. At the end, the supplemented group did not differ from the placebo group in testosterone levels or muscle mass or strength gains. However, the supplemented group had significantly higher levels of estrogens, once again raising concerns about the effects of these supplements long-term.

Taking plant steroids has a significant problem in its theoretical basis. Manufacturers of DHEA and other steroids use a complicated series of chemical reactions to convert plant steroids into steroids found in the human body. There is significant evidence that the human body cannot do these reactions and therefore cannot convert plant steroids into human steroids.[62] In addition, plant steroids are poorly absorbed from the human intestinal tract and may elicit hormonal changes that actually reduce endogenous testosterone production.[63]

Conclusion

Powerful pressures exist in the sports world today. The rewards for successful performance are increasing. Athletes are under greater and greater pressures, at younger and younger ages, to maximize their performances. Little wonder they are turning to chemical methods to enhance their natural endowment and their hours of training and practice. However, sporting bodies like the IOC and NCAA have banned those ergogenic aids that actually work.[34,35] Athletes who do not abide by the ethical standards of fair competition will find themselves barred from competition if they fail blood tests.

Some athletes turn to natural supplements in the hope of legally obtaining ergogenic aids. If these substances contain anabolic agents, they will still fail the blood doping tests. However, the danger with dietary supplements often goes beyond the mere fact that the substances are ineffective and carry significant risks of adverse effects. The quality of many of these products also is questionable. Although the pressure to try ergogenic aids is understandable, the ethics of good sportsmanship insist on limiting performance enhancement to making the most of one's natural gifts, hard work, and proper nutrition. While some question whether these are old ethics for a time gone by, they help protect the health of those who most exemplify the amazing capabilities of the human body. How ironic it is that in trying to get the most out of their bodies, some appear unconcerned about the effects of what they put into their bodies. Physicians should do their best to help promote the health of athletes by giving them reliable information about the ergogenic aids available as dietary supplements. ❖

Dr. O'Mathúna is Professor of Bioethics and Chemistry at Mount Carmel College of Nursing in Columbus, OH.

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Supplement to *Alternative Medicine Alert*
May 2001

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

Calcium

EIGHT MILLION AMERICAN WOMEN AND 2 MILLION AMERICAN MEN HAVE OSTEOPOROSIS. Another 18 million have low bone density, which increases their risk of osteoporosis. Although many Americans are aware of the role calcium plays in maintaining bone health, few receive recommended amounts of calcium from their diet. In recent years, our knowledge of the role of calcium in other diseases and conditions (e.g., colon cancer and premenstrual syndrome) has expanded, reinforcing the need for adequate calcium intakes.

Dietary Reference Intakes (DRI)

210 mg/d for children 0-6 mo
270 mg/d for children 7 mo-1 y
500 mg/d for children 1-3 y
800 mg/d for children 4-8 y
1300 mg/d for children 9-18 y
1000 mg/d for adults 19-50 y
1200 mg/d for adults 51 y and older

Food Sources

Dietary sources of calcium include dairy products, kale, broccoli, calcium-enriched citrus juices, mineral water, canned fish with bones, and tofu.

Mechanism of Action

- Bones and teeth contain more than 99% of the body's calcium. Calcium in bone is a reserve source of calcium that can be mobilized to maintain extracellular calcium concentrations.
- Calcium is involved in intracellular regulation, enzyme activation, hormone secretion, initiation of DNA synthesis, and muscle cell function. In heart muscle and nerve terminals, calcium channels open when membranes are depolarized and stored calcium is released.
- Calcium is lost in varying amounts through the feces, urine, sweat, and sloughed skin cells.

Calcium Solubility, Bioavailability, and Absorption

- Although some studies have found calcium citrate to be more bioavailable and absorbable than calcium carbonate,[1-3] these studies were performed on fasting patients, which can lead to erratic absorption.[4] When ingested as part of a meal, calcium carbonate is equally well absorbed.[5]
- Calcium absorption is not determined exclusively by the solubility of the calcium salt, but varies with age, environmental and dietary conditions, vitamin D status, and race. Average absorption ranges from 25% in infants to 60% in young adults, and generally decreases throughout adulthood.
- Calcium exhibits threshold absorption. Below the threshold, increased calcium intake improves response; above the threshold, increased calcium intake has no effect. It is recommended that patients split doses above 600 mg.
- Calcium content of various preparations: carbonate, 40%; tricalcium phosphate, 38%; dicalcium phosphate, 31%; bone meal, 31%; oyster shell, 28%; dolomite, 22%; citrate, 21%; lactate, 13%; gluconate, 9%; glubionate, 6.5%.[6]

Clinical Uses

- To reduce the risk of colorectal cancer.
- To treat diarrhea and rectal epithelial hyperproliferation following intestinal bypass.

- To treat hypocalcemia, chronic hypoparathyroidism, and osteomalacia.
- To prevent and treat osteoporosis, rickets, and latent tetany.
- To bind phosphate in renal failure (calcium carbonate and calcium acetate).
- To treat indigestion (calcium carbonate).
- To reduce fluoride levels in children.
- To treat hypertension.
- To treat premenstrual syndrome.
- To increase fetal bone mineralization when taken by pregnant women with low dietary calcium intake.
- To prevent pregnancy-related hypertension and preeclampsia.
- To prevent ischemic stroke.

Adverse Effects/Toxicity

- Routine dietary intake and supplementation in recommended doses are not associated with significant adverse effects; however, gastrointestinal irritation, belching, flatulence, and constipation are common complaints.
- Calcium carbonate can cause acid rebound.
- Intakes exceeding 2 g/d can increase the risk of kidney stones and renal damage; this dose may be lower in patients with idiopathic hypercalciurea.
- Prolonged ingestion of large amounts (greater than 20 g/d) of calcium carbonate can cause hypercalcemia, milk-alkali syndrome, nephrocalcinosis, and renal insufficiency.
- Ingestion of calcium chloride may cause gastrointestinal hemorrhage.
- Epidemiological evidence suggests that high dietary calcium intake might increase the risk of prostate cancer.

Interactions/Nutrient Depletion

- Calcium absorption is increased by: concomitant administration of vitamin D and estrogen.
- Calcium absorption is decreased by: concomitant administration of fluoroquinolones and tetracyclines; mineral oil; stimulant laxatives; wheat bran; and high-phytate soybeans.
- Concomitant calcium administration decreases the absorption of: iron, zinc, magnesium, bisphosphonates, fluoroquinolones, thyroid hormones, and tetracyclines.
- Concomitant use of thiazide diuretics and moderately large amounts of calcium carbonate increase the risk of milk-alkali syndrome.
- Urinary calcium excretion is increased by: concomitant administration of thiazide diuretics; aluminum and magnesium salts; thyroid hormones; and high sodium intake.
- Pretreatment with intravenous calcium gluconate can prevent or reduce the hypotensive effects of intravenous verapamil without affecting the antiarrhythmic effects of verapamil.
- Use of corticosteroids can cause calcium depletion and osteoporosis.
- Calcium carbonate use can alter the results of: serum gastrin, serum lipase, and bone mineral density tests.
- Calcium gluconate use can alter the results of: serum glucose, plasma 11-hydroxycorticosteroids, urinary 17-hydroxycorticosteroids, plasma insulin, I-131 uptake, and serum magnesium tests.
- Hyperparathyroid activity predisposes individuals to increased calcium absorption.
- Calcium use in individuals with high serum phosphate levels should be monitored carefully to prevent precipitation of calcium phosphate and soft tissue calcification.
- Renal insufficiency predisposes individuals to reduced calcium absorption.
- Sarcoidosis results in increased risk of excessive calcium absorption and hypercalcemia.
- Smoking decreases calcium absorption.

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