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Oral L-arginine for Improving Vascular Function in Hypercholesterolemia, PVD, and Atherosclerotic Heart Disease

By Matthew J. Sorrentino, MD

DURING PHYSICAL ACTIVITY BLOOD FLOW TO THE HEART MUST increase to meet the metabolic needs of the heart muscle. L-arginine is an amino acid that has recently been touted and tested for its effect on blood flow to the heart. These tests have yielded promising results: L-arginine is not all hype, and may actually improve vascular function.

Background

Coronary blood flow is regulated by both local and systemic factors. Patients with hypercholesterolemia and atherosclerotic heart disease, however, develop abnormal function of their arteries. Instead of vasodilating, diseased arteries tend to vasoconstrict, decreasing blood flow and increasing the potential for clot formation. Ideally, treatment of atherosclerotic disease should heal dysfunctional endothelium and restore normal vascular reactivity. L-arginine, either by supplementation or from the diet, may be one treatment for improving the health of the vasculature.

Physiology

The endothelial cell layer lining arteries was previously thought to be an inert barrier that separated the blood from arterial smooth muscle. In the early 1980s it was discovered that an intact endothelium was necessary for vasodilation of arteries. A substance named endothelium-derived relaxing factor (EDRF) was proposed as an agent synthesized by endothelial cells that helped regulate arterial tone. Numerous substances have been shown to stimulate EDRF release from endothelial cells through activation of cell surface receptors or ion channels. These stimulators include acetylcholine, bradykinin, histamine, ADP, ATP, thrombin, substance P, and physical factors such as blood flow and pulse pressure.

Mechanism of Action

EDRF is most likely nitric oxide (NO) or a complex containing it.[1] The enzyme nitric oxide synthase generates NO from the amino acid L-arginine. NO is responsible for vasodilator tone in the coronary arteries and the regulation of blood pressure in the systemic arteries. Exogenous nitroglycerin acts through the same pathway to cause vasodilation. NO has also been shown to inhibit platelet aggregation and adhesion and may have a role in preventing thrombotic complications.[2]

Strategies for restoring endothelium-dependent vasodilation and allowing healing of dysfunctional coronary arteries are now being developed. Cholesterol lowering has been shown to improve endothelial function and clinically to reduce ischemia.[3-5] Other strategies include preventing EDRF degradation through free radical scavengers (superoxide dismutase) or replenishing the supply of EDRF by supplementation of the precursor L-arginine.

Animal Studies

L-arginine supplementation may be antiatherogenic. Dietary supplements of L-arginine in hypercholesterolemic rabbits block the progression of intimal thickening in coronary arteries, carotid arteries, and the aorta, and preserve normal endothelium-dependent relaxation.[6-8] These antiatherogenic effects have yet to be demonstrated in humans.

Clinical Studies

Early studies have shown that intravenous administration of L-arginine infusion acutely improved endothelium-dependent vasodilation[9] and oral L-arginine (7 g tid for a four-week treatment period) supplementation improved vasodilation.[10]

L-arginine has been shown to improve coronary blood flow both in the epicardial coronary arteries and in the microcirculation. Short-term intracoronary infusion of L-arginine improved the endothelial response to acetylcholine in hypercholesterolemic subjects.[11] Intravenous L-arginine has been shown to attenuate the paradoxical vasoconstrictor response in atherosclerotic coronary arteries but only in arteries with early lesions and not in arteries with advanced lesions.[12]

L-arginine also improves coronary blood flow in patients with angiographically normal coronary arteries but abnormal responses to acetylcholine.[13] These patients are thought to have either impaired coronary microvasculature or diffuse coronary artery atherosclerosis. Oral L-arginine has been shown to improve coronary blood flow in this group of patients and improve chest pain symptoms.[14] Cardiac transplant patients also exhibit diffuse endothelial dysfunction that can be reversed by intravenous infusion of L-arginine.[15] This improvement is more likely to occur in vessels without intimal thickening. Microcirculatory functional improvement indicates that early dysfunction is more likely to respond than advanced disease.

Platelet Aggregation. Platelets from hypercholesterolemic individuals show increased aggregability on aggregometry studies with collagen. Supplementation with 8.4 g/d of L-arginine for two weeks modestly decreased platelet reactivity,[16] presumably through increased synthesis of NO, known to inhibit platelet adherence and aggregation.[2]

Nitroglycerin, an exogenous nitrate, also inhibits platelet reactivity. Both platelet-derived and endothelial-derived NO have been shown to regulate platelet responsiveness. The endothelium is thought to condition platelets as they flow through the vasculature increasing cyclic GMP and decreasing aggregability.

Use in Peripheral Vascular Disease. Boger and colleagues performed a double-blind, controlled study using prolonged intermittent infusion therapy with L-arginine (two intravenous infusions daily of 8 g L-arginine for

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three weeks) in patients with intermittent claudication.[17] The L-arginine patients experienced improved endothelium-dependent vasodilation in the femoral arteries and a significant improvement in pain-free walking distance. The same group of investigators infused L-arginine into individuals with critical limb ischemia from advanced peripheral vascular disease, increasing femoral artery blood flow.[18]

Use in Heart Failure. A randomized, double-blind, placebo-controlled study in moderate to severe heart failure showed an improvement in walking distance on the six-minute walk test in individuals after six weeks of oral L-arginine supplementation.[19] In another study, intravenous infusion of 20 g of L-arginine over a one-hour period increased stroke volume and cardiac output without a change in heart rate, and decreased arterial blood pressure and systemic vascular resistance. These hemodynamic changes return to baseline within an hour of cessation of the infusion.[20]

Preparations and Dietary Sources

L-arginine is a semi-essential amino acid and can be synthesized in the body. It is considered semi-essential because throughout most of life, people synthesize enough L-arginine. However, supplementation may be required during periods of rapid growth in childhood. L-arginine is present in protein found in meats, nuts, milk, cheese, eggs, fish, and beans. (*See Table 1 for foods rich in L-arginine.*) L-arginine can stimulate the pituitary gland to release growth hormone and therefore has become a popular supplement for muscle building among athletes.

L-arginine is available in 500 mg capsules. Typical doses used in vascular studies have been 3 g tid. Bottles of 100 capsules cost between $10 to $15. Recently, Cooke Pharma has marketed a protein bar (HeartBar™) that contains 3 g of L-arginine per bar. The bars also contain supplements of vitamins C, E, B_6, B_{12}, folic acid, and niacin. The original- and cranberry-flavored bars cost between $1.19 and $1.79 each.

Side Effects

L-arginine is usually well-tolerated but can cause side effects such as nausea and diarrhea. In diabetics, L-arginine may raise sugar levels, which potentially could cause changes in medication requirements.

Conclusion

L-arginine supplements either as capsules or a protein bar are effective in raising L-arginine levels and can give short-term improvement in vascular reactivity. The restoration of normal vascular reactivity can reduce cardiac symptoms and vascular events. The

Table 1

Foods rich in L-arginine

Food	Serving Size	L-arginine Content	Food	Serving Size	L-arginine Content
Whelk (sea snail)	3 oz	4198 mg	Broiled pork chop	3.5 oz	1785 mg
Dried spirulina (seaweed)	3.5 oz	4147 mg	Clams	3 oz	1585 mg
Dry roasted soybeans	½ cup	2641 mg	Pumpkin or squash seeds	1 oz	1536 mg
Roasted venison	3.5 oz	2175 mg	Alaskan king crab	3 oz	1437 mg
Roasted light meat turkey without skin	3.5 oz	2086 mg	2% fat cottage cheese	1 cup	1417 mg
Tuna salad	½ cup	1982 mg	Sockeye salmon	3 oz	1390 mg
Spiny lobster	3 oz	1959 mg	Chickpeas	1 cup	1369 mg
Extra lean ground beef (well done)	3.5 oz	1915 mg	Firm tofu	½ cup	1323 mg
Roasted chicken (light meat without skin)	3.5 oz	1864 mg	Dried pignolia (pine) nuts	1 oz	1323 mg
Octopus	3 oz	1851 mg	Boiled crayfish	3 oz	1300 mg
			Freshwater bass	3 oz	1230 mg
			Hummus	1 cup	1109 mg
			Black beans	1 cup	944 mg

Adapted from: Pennington JA. *Bowes and Church's Food Values of Portions Commonly Used.* 17th ed. Philadelphia, PA: Lippincott-Raven Publishers; 1998:316-382.

substrate L-arginine appears to increase production of NO improving vascular responsiveness. A major limitation of the use of exogenous nitrates has been the development of nitrate tolerance that can occur soon after the initiation of therapy. Nitrate tolerance seems to occur because of the loss of the vascular effects of the drugs although the exact mechanism is unknown.[21] L-arginine therapy may have the same limitations as exogenous nitrates because it works through similar mechanisms. Long-term studies and an evaluation for tolerance have not been done.

Recommendation

A diet rich in the amino acid L-arginine may help patients with hypercholesterolemia, and patients with atherosclerotic disease. Because hypercholesterolemia can impair vascular function, the protein rich in L-arginine should not come from red meats but instead should come from seafood, poultry, nuts, and beans. Diet can supply an adequate amount of L-arginine and is the recommended method of supplementation. ❖

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Astragalus as an Adjunctive Therapy in Immunocompromised Patients

By Teresa Klepser, PharmD and Nicole Nisly, MD

MANY PATIENTS WHO ARE IMMUNOCOMPROMISED BY diseases such as cancer, acquired immunodeficiency syndrome (AIDS), and lupus want to take an active role in controlling their disease. Herbs allow patients to take control without the advice of healthcare professionals. Self-administration of herbs such as astragalus, however, may be dangerous and may delay more useful help.

Historical Indications and Mechanisms

Astragalus (*Astragalus membranaceus*), also known as huang qi or huang chi, has been used in China for at least 2,000 years.[1] Astragalus grows in northern China, Japan, and Korea; the most potent and expensive variety originates in China.[2] The medicinal part of the plant is the yellowish-brown root which is sold in 15-20 cm slices.[2] The yellowish-white marrow inside the root reportedly tastes like licorice.[2]

According to the Chinese materia medica, astragalus is recommended as an adaptogenic or tonic herb: It is "Qi tonifying." It is believed to increase the circulation of wei-chee (a protective energy) around the surface of the body.[2] Astragalus is also believed to enhance immunity by protecting the body from the Six Evils of aberrant—wind, cold, heat, dampness, dryness, and fire.[2] The Six Evils are believed to be the primary causes of disease. For example, wind evil is the carrier of aberrant energies associated with summer and autumn.[2] Symptoms of wind injury would include fever and chills, coughs, and sinus congestion.[2] Symptoms are also diagnosed in terms of yin and yang polarity.[2] Fever would be considered a yang symptom, whereas chills would be considered a yin symptom.[2]

In traditional Chinese medicine, astragalus is prescribed for general debilities, chronic illnesses, and to increase overall vitality.[3] Astragalus has also been recommended for "spleen-Qi deficiency" symptoms, general respiratory disorders (i.e., colds, flu, and shortness of breath), painful joints, numbness, edema, and for the promotion of healing of chronic sores, abscesses, and wounds.[1,3,4] The spleen is believed to be the origin of Qi (vital energy) and blood. Therefore, if the spleen were not working properly, a person would be deficient in Qi and blood, and would become weak and tired.[5] Spleen-Qi deficiency is believed to be the most common cause of chronic tiredness; symptoms include night sweating, fatigue, diarrhea, and loss of appetite.

Components

The root of the astragalus plant is considered to contain the medically important components. The biologically active compounds include a polysaccharide, saponins, coumarins, and flavonoids.[6]

Mechanism of Action

Little data exist regarding overall mechanism of action. The polysaccharide component possesses antirhinoviral activity and potentiates interferon activity, considered useful in treating the common cold and influenza.[6] The saponins activate the peritoneal macrophages and enhance tissue necrotizing factor (TNF) activity, which may be helpful in the treatment of autoimmune disorders.[6] Some data suggest astragalus may have antitumor activity mediated by interleukin-2.[7] Other research has suggested that astragalus has an antioxidant effect, given the presence of isoflavones.[8]

Laboratory Studies

Much data regarding the immunostimulatory effects of astragalus have been generated using animal models. Unfortunately, most of the studies are published in Chinese medical journals[9-12] and astragalus often is combined with other herbs such as ginseng, schisandra, angelica, codonopsis, echinacea, and/or licorice.[2,4]

Astragalus has been reported to reverse cyclophosphamide-induced immunosuppression in mice and rats.[13-15] It has also been reported to exert antitumor effects in murine models of renal cell carcinoma via enhancement of phagocyte and lymphokine-activated killer cells.[16] Sun et al evaluated the effect of astragalus and another traditional Chinese medicinal herb, *Ligustrum lucidum*, on mononuclear cells from 19 cancer patients and 15 normal healthy donors. Cancer patients' mononuclear cells were incubated with either aqueous solutions of astragalus or ligustrum; healthy donor cells were incubated without an herbal solution. The number of mononuclear cells incubated with astragalus or ligustrum significantly increased compared to the mononuclear cells that were untreated.[17]

Chu et al evaluated the effect of astragalus on

mononuclear cells isolated from healthy donors and 13 oncology patients.[18] Among eight of the oncology patients, the number of mononuclear cells treated with fractionated astragalus increased compared to the untreated mononuclear cells and also to the healthy donor mononuclear cells.

Clinical Studies

A recent case report describes a 15-year-old male with Stage IIA nodular sclerosing Hodgkin's disease who chose to treat his cancer with Matol Biomune OSF Plus instead of the traditional therapy of multiagent chemotherapy and low-dose irradiation. Matol Biomune OSF Plus contains astragalus, dairy colostrum, and whey. After the patient started taking Matol Biomune OSF Plus, the disease progressed into Stage IIB. Since the disease significantly progressed, the patient elected to discontinue Matol Biomune OSF Plus and start the traditional therapy of doxorubicin, etoposide, and bleomycin. The report does not state whether the patient's disease continued to progress.[19]

One Chinese study evaluated the effect of two concentrations of astragalus preparations in 115 cases of leukopenia. Patients received either 5 g or 15 g of astragalus twice daily. Both treatments had a significant increase in white blood cell count. However, the group that received the more concentrated astragalus preparation (15 g) had a significantly higher white blood cell count. There appears to be a dose-dependent relationship. Unfortunately, the abstract is the only description of this study in English.[20]

Another Chinese study compared the effect of astragalus administration among 28 patients with systemic lupus erythematosus to a group of normal controls also treated with the herb. It was reported that the astragalus-treated systemic lupus erythematous patients exhibited significantly decreased natural killer cell activity.[21] Again, unfortunately, the abstract is the only description of this study in English.

Fifty-four cases of small cell lung cancer treated with chemotherapy, radiotherapy, immunotherapy, traditional Chinese medicine, and other adjuvants were evaluated in another Chinese study. Chemotherapy consisted of vincristine, cyclophosphamide, methotrexate, and carmustine. Traditional Chinese medicine included Asiatic ginseng leaf and *Astragalus membranaceus* root.

In this study, an overall treatment response of 98.1% was achieved. Treatment response was not defined in the abstract. Fifty-nine percent attained a complete response and 38.9% achieved partial response. Survival rates improved, especially with long-term (more than two years or 10 courses), short-interval, combined treatment. By using the combined therapies noted above, 10 of 12 patients reportedly gained from 3-17 years of survival.[22] Again, unfortunately, the abstract is the only English description of this study.

Adverse Effects

No reports of astragalus-related adverse events could be identified in the published English literature in the following databases: MEDLINE, CINAHL, Current Contents, Cochrane, CancerLit, HealthStar, IBIDS, PubMed, National Center of Complementary and Alternative Medicine, and Alternative and Complementary Medicine Center HealthWorld Online. Astragalus may lower blood pressure and may cause diuresis.[23] Overdosing may cause immunosuppression.[23]

Contraindications/Precautions

No contraindications or precautions are known.[2] However, some Astragalus species appear to be toxic to livestock. Case reports of livestock grazing on *Astragalus* and *Oxytropis* species note irreversible neurologic toxicity because of the locoweed toxin, swainsonine. The toxins are only in the above-ground parts of the plants, not in the roots, which are the medicinal part of the plant.[24,25]

Drug Interactions

It is currently recommended that astragalus not be taken with opiates. It is unknown if astragalus will interact with any immunosuppressive medications such as cyclosporin. Herbalists caution against the use of astragalus in patients taking immunosuppressive medications.[24]

Formulation

Astragalus is available in a variety of preparations at varying dosages. Formulations include tinctures, tablets, capsules, powdered herb, and extracts. Astragalus is often included in combination herbal products that also frequently contain ginseng, schisandra, angelica, codonopsis, echinacea, and/or licorice.[2,4] Fu Zheng is an herbal combination containing astragalus that some Chinese herbalists prescribe for patients undergoing chemotherapy and radiotherapy.

Dosage

In the practice of traditional Chinese medicine, astragalus tea is prepared using 9-15 g of the dried, sliced root simmered in water for several hours.[4] A liquor may also be made by steeping 80-100 g of sliced root in one liter of spirits for two to three months. Patients are instructed to consume 1 oz of the liquor twice daily either straight

or diluted with 1-2 oz of water.[2] Some Chinese herbalists recommend adding the tongue-depressor shaped slices of astragalus root to medicinal soups, allowing them to flavor meals with their immunostimulating properties.

Capsules marketed in the United States generally contain 500 mg of dried herb. In this form, the recommended dose is 1,000 mg tid.[4] Unfortunately, astragalus products are not standardized to a specific active ingredient.

Conclusion

Clinical evidence to support the use of astragalus for any clinical condition is scarce in the reported English-speaking literature.

Recommendation

Until more literature appears in the English language, *Astragalus membranaceus* should not be considered as an adjunct therapy for immunocompromised patients. ❖

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Intercessory Prayer and ICU Outcome

By V. Jane Kattapong, MD, MPH

"Pray for my soul. More things are wrought by prayer
Than this world dreams of."

Alfred Lord Tennyson
"The Passing of Arthur"
Idylls of the King

LAY BELIEFS ABOUT THE ETIOLOGY OF ILLNESS DIFFER substantially from scientific explanations. Dismissing lay beliefs simply because we do not understand or share them, however, is setting ourselves up for failure. Most of what drives alternative medicine is not science, but belief. It makes special sense, then, to investigate faith and its effects on patients' medical problems.

Intercessory Prayer

In accordance with a belief in God's power to bring good health, some patients believe that their own prayers may bring improvement in their own illness. However, what happens when others pray for patients? Some believe that intercessory prayer (IP), or praying for the benefit of others, can help the healing process.[1,2] This belief is not unique to Judeo-Christian religion, but is also an integral part of the healing process in Native American medicine,[3] and figures prominently in Buddhist and other Eastern religions as well.

Prevalence

Few people can say that they have never offered up silent, urgent prayers while experiencing stomach-churning turbulence aboard a bouncing airplane, or in other instances of perceived dire need. Many patients turn to prayer for reassurance, strength, and guidance when they are ill.

The prevalence of prayer in the United States is quite high. Ninety-five percent of Americans believe in God, more than 50% pray daily, and more than 40% attend church weekly.[4] Little is known, however, about the prevalence of IP.

Techniques

IP is usually performed by individuals who are acquainted with the patient or with someone who knows the patient. Often IP is performed by individuals who have close personal ties to the patient. Frequently church members request that other members of the congregation perform IP for a family member or friend.

Mechanism of Action

The effect of IP on illness has largely been ignored in the medical literature, perhaps because it is quite difficult to postulate a reasonable scientific explanation for any effects.

One lay theory about the etiology of health and illness is the explanation of "God's power," in which "health is a product of 'right living,' spiritual well-being and God's power."[5] Belief in the power of a Superior Being, or God, to influence and control health and illness is widespread worldwide. One way to communicate with God is through prayer. According to Webster's Collegiate Dictionary, prayer is "a spiritual communion with God or an object of worship, as in supplication, thanksgiving, or adoration."[6] Almost without exception, this spiritual communion, or prayer, has been a meaningful component of all cultures to date.

Medical Explanations

Medical explanations have been proposed for health benefits associated with prayer and religiousness. Levin believes that personal religious beliefs may strengthen coping skills and decrease stress, and thereby decrease morbidity and mortality in patients with such diseases as hypertension, heart disease, and cancer. These direct health benefits may occur through psychoneuroimmunologic mechanisms, and may result in decreased activation of the hypothalamic pituitary axis.[7]

But it becomes more difficult to postulate scientific explanations for health benefits as the individual

performing the prayer becomes further removed from the patient. Far fewer psychoneuroimmunological mechanisms can reasonably be invoked when the individual performing the prayer is not the patient. And when the individual performing the prayer is unknown to the patient, even fewer may be offered. Any health benefits resulting from the efforts of an unseen, unrevealed third party can be considered scientifically enigmatic.

Clinical Studies

A literature search revealed only one blinded study of the effects of IP in a critical care setting. In this study, all patients admitted between August 1982 and May 1983 to the coronary care unit of the San Francisco General Hospital were eligible for study entry.[1] Although 393 patients chose to participate, 57 declined because of personal reasons, religious convictions, or unwillingness to sign the consent form. A computer-generated list was used to assign patients randomly to customary care, or customary care plus IP. The intercessors (those praying on behalf of the patients) were members of local Protestant or Roman Catholic churches. Prior to involvement in this study, all intercessors reported daily devotional prayer and active church membership.

Each patient was randomly assigned to three to seven intercessors, who prayed daily outside the hospital until discharge. The site in which the IP was performed was not specified. Each intercessor was given information including the patient's first name, diagnosis, general condition, and updates in status. Intercessors prayed for rapid recovery and for prevention of complications and death. Patients in the prayer and non-prayer groups were similar with respect to cardiac disease severity, age, and gender.

By the time of discharge, on univariate analysis, the prayer group was less likely than the control group to have experienced congestive heart failure, cardiopulmonary arrest, and pneumonia, or to have required diuretics, antibiotics, or intubation and mechanical ventilation ($P < 0.05$). Multivariate analysis demonstrated that the group receiving IP was significantly less likely to require ventilatory support, antibiotics, or diuretics ($P < 0.0001$). Based on outcome, defined criteria were used to grade hospital course as good, intermediate, or bad. Good outcome was determined to have occurred in 85% of the intercessory prayer group vs. 73% of the control group. Intermediate outcome occurred in 1% of the prayer group and 5% of the controls. Bad outcome occurred in 14% of the prayer group and 22% of the controls. A chi-square analysis demonstrated significantly better outcome in the prayer group ($P < 0.01$). No information was available about the religiousness of the patients.

Prayer in Other Illness Settings

To determine the effect of religious affiliation on obstetric outcome, King examined 1,919 obstetric records at a university medical center in North Carolina, and obtained demographic information, prenatal history, labor and delivery records, and religious affiliation.[8] "Mainline" Christians (defined as Catholics, Methodists, and Episcopals) had the lowest neonatal intensive care unit admission and maternal complication rates. Evangelical Christians (Baptists, Free Will Baptists, Pentecostals, and Holinesses) had intermediate rates. Rates were highest for patients with no religious preference. These complication rates were significantly lower in the two Christian groups than in the non-religious group ($P < 0.05$).

In a review, Sherrill discusses the role of religion in the recovery process for adult burn patients.[9] Although only a review of the literature and anecdotal evidence in the form of case reports are presented, she concludes that religiousness may improve the recovery process for burn patients. She believes that further investigation into the role of religion in burn recovery is warranted.

In contrast, a review of the effectiveness of IP on improvements to health problems and an evaluation of the effectiveness of IP on wound healing found little significant benefit associated with IP.[10,11] The authors found that the results of these studies were inconclusive.

Conclusion

Little attention has been devoted to the effects of IP on the recovery process. However, based on one randomized, double-blind study, praying for the benefit of others appears to confer patient benefits. Specifically, good outcome after admission to a coronary care unit was found to be more likely in the group receiving IP.

Recommendation

Intercessory prayer is an intervention that can easily be offered to every ICU patient. In fact, it can easily be offered to every patient with any degree of illness. Because it is unlikely that IP would ever hurt, and might help, there is no reason to dissuade interested patients from it. Whether IP may be recommended to patients depends on patient interest and better data. Although we have, at best, an incomplete scientific explanation for the benefits of prayer, we can "take it on faith" that prayer may improve the healing process. ❖

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CME Questions

23. L-arginine is the precursor of endothelium-dependent relaxation factor.

a. True
b. False

24. L-arginine supplementation has been shown to:

a. improve vasodilation.
b. decrease platelet reactivity.
c. increase pain-free walking distance in patients with intermittent claudication.
d. increase femoral artery blood flow in patients with critical limb ischemia.
e. All of the above.

25. For which of the following is astragalus touted to offer any benefit?

a. Impotence
b. Premenstrual syndrome
c. Nausea
d. Cancer
e. Kidney disease

26. Which of the following drugs may interact with astragalus?

a. Bromocriptine
b. Haloperidol
c. Aspirin
d. Atenolol
e. Morphine

27. Psychoneuroimmunologic mechanisms that may be involved in health benefits of intercessory prayer are:

a. decreased activation of the hypothalamic pituitary axis.
b. decreased platelet aggregation.
c. serotonin-modulation.

28. Outcome of intercessory prayer (IP) for CCU patients is:

a. good outcome in 85% of the IP group and 73% of the control group.
b. good outcome in 1% of the IP group and 5% of the control group.
c. good outcome in 14% of the IP group and 22% of the control group.

In Future Issues:

Phytosterols and Cholesterol

Phytoestrogens and Osteoporosis

Reiki as Adjunct to Conventional Care

Special Report: Changing Eating and Fitness Habits

With Comments from John La Puma, MD, FACP

DHEA Replacement in Women with Adrenal Insufficiency

Arlt W, et al. Dehydroepiandrosterone replacement in women with adrenal insufficiency. *N Engl J Med* 1999;341:1013-1020.

THE PHYSIOLOGIC ROLE OF DEHYdroepiandrosterone (DHEA) in humans is still unclear. Adrenal insufficiency leads to a deficiency of DHEA; we therefore investigated the effects of DHEA replacement in patients with adrenal insufficiency.

In a double-blind study, 24 women (mean age 42 +/-9 years) with adrenal insufficiency of a mean 9 +/-2 years duration received in random order 50 mg of DHEA orally each morning for four months and placebo daily for four months, with a one month washout period. All women continued to take standard medication, including estrogen-progestin replacement therapy, if appropriate. We measured serum steroid hormones, insulin-like growth factor I, lipids, and sex hormone-binding globulin. We evaluated well-being and sexuality with the use of validated psychological questionnaires and visual-analogue scales, respectively. The women were assessed before treatment; after one and four months of DHEA treatment, and placebo treatment; and one month after the end of the second treatment period.

Treatment with DHEA raised the initially low serum concentrations of DHEA, DHEA Sulfate, androstenedione, and testosterone into the normal range; serum concentrations of sex hormone-binding globulin, total cholesterol, and high density lipoprotein cholesterol decreased significantly.

DHEA significantly reduced serum total cholesterol and HDL concentrations. DHEA significantly improved overall well-being as well as scores for depression and anxiety. For the global severity index, the mean (+/-SD) change from baseline was -0.18 +/-0.29 after four months of DHEA therapy, as compared with 0.03 +/-0.29 after four months of placebo (P = 0.02). As compared with placebo, DHEA significantly increased the frequency of sexual thoughts (P = 0.0006), sexual interest (P = 0.002), and satisfaction with both mental and physical aspects of sexuality (P = 0.0009 and P = 0.02, respectively). Five of the 24 women reported greasy skin, acne, and increased growth of body hair.

We conclude that DHEA improves well-being and sexuality in women with adrenal insufficiency.

COMMENT

This well-designed, carefully performed, double-blind study by German investigators raises the bar for evidence-based research in alternative medicine. As O'Mathúna reported last month, the FDA categorized DHEA as an unapproved drug in 1985, making it available only by prescription. The 1994 Dietary Supplement Health and Education Act reclassified it as a dietary supplement. Since then, its popularity has exploded. Unfortunately, DHEA supplementation cannot be recommended as an evidence-based therapeutic option for relief of menopausal symptoms. (See *Alternative Medicine Alert*, October 1999, pp. 113-116.)

But DHEA did wonders for constitutional signs of adrenal insufficiency. And its supplementation is pharmacologic replacement: The adrenal cortex does normally secrete DHEA and DHEA Sulfate. Supplemental corticosteroids are lifesaving in this disease; supplemental DHEA appears to be quality-of-life-saving.

DHEA did not raise estrogen concentrations, did lower HDL levels, and vastly improved the sex lives of these women. As an androgen precursor, could DHEA do so for men too?

DHEA has been evaluated in a double-blind, randomized trial with 40 men (mean age, 56 years), healthy except for erectile dysfunction. The men used 50 mg DHEA daily. Drop-out was high (three taking DHEA; seven on placebo), but those taking DHEA scored higher on all five domains of the International Index of Erectile Function (Reiter WJ, et al. Dehydroepiandrosterone in the treatment of erectile dysfunction: A prospective, double-blind, randomized, placebo-controlled study. *Urology* 1999;53:590-595).

Whether DHEA should be considered for patients consigned to prolonged high-dose glucocorticoid therapy and patients with postmenopausal osteoporosis awaits similar trials. Healthy men and women will soon order the stuff by the truckload, like Viagra, only cheaper.

Limitations to this study include its short duration and its exclusion of men. It is logical but not demonstrated that the risk of breast (and prostate) cancer increases with DHEA supplementation.

Recommendation

Small doses of DHEA should be part of a therapeutic regimen in primary and secondary adrenal insufficiency. Patients should be closely monitored and screened for androgen-related problems, including cancers. ❖

Beta-carotene Supplementation and Diabetes Risk

Liu S, et al. Long-term beta-carotene supplementation and risk of type 2 diabetes mellitus: A randomized controlled trial. *JAMA* 1999;282:1073-1075.

RECENT DATA SUGGEST A PROTECTIVE role of carotenoids in the development of type 2 diabetes mellitus (DM), possibly via an antioxidant effect, but no

randomized trial has directly assessed the efficacy of beta-carotene to prevent type 2 DM.

We enrolled a total of 22,071 healthy U.S. male physicians aged 40-84 years in a randomized, double-blind, placebo-controlled trial from 1982 to 1995. Subjects received beta-carotene (50 mg on alternate days) or placebo. More than 99% of the participants had complete follow-up of median duration 12 years.

A total of 10,756 subjects were assigned to beta-carotene and 10,712 were assigned to placebo. Incidence of type 2 DM did not differ between groups; 396 men in the beta-carotene group and 402 in the placebo group developed type 2 DM (relative risk 0.98; 95% confidence interval, 0.85-1.12). The lack of association between beta-carotene supplementation and incidence of type 2 DM persisted despite multivariate adjustment. There was no evidence of benefit when the period of risk was subdivided into years of follow-up or increasing duration of treatment.

In this trial of apparently healthy men, supplementation with beta-carotene for an average of 12 years had no effect on the risk of subsequent type 2 DM.

COMMENT

Most of the data we have about carotenoids (a category which includes the carotenes, lycopene, cryptoxanthin, and lutein) come from extrapolating backward from brightly colored fruits and vegetables. Findings from the Third National Health and Nutrition Examination Survey (Ford ES, et al. Diabetes mellitus and serum carotenoids. *Am J Epidemiol* 1999;149:168-176), for example, showed that among 1,665 subjects, serum beta-carotene level and degree of glucose intolerance were directly and linearly correlated.

The investigators matched their groups clinically: Even their body mass indices were identical at baseline (24.9 Kg/m^2). Reported adherence to the beta-carotene regimen was 85% after five years and 78% after 12 years.

In this re-analysis of the Physicians' Health Study, the equivalent of two carrots a day (according to the authors' other work, higher than the average American consumption) of beta-carotene did not prevent diabetes. But these subjects did not receive carrots—they received supplements. And beta-carotene supplements have been associated with an increased incidence of death from lung cancer and stroke, or no change at all.

Weaknesses of this study include the fact that the participants self-reported their diagnoses, and medical records were not checked. (Diagnosis denial is an effective coping mechanism among many patients until reality intervenes.)

Recommendation

Intensified, concentrated components of food, such as beta-carotene, probably do have a medicinal use. Beta-carotene for diabetes prevention is not one of them. Carrots, mangoes, and habañeros are likely to be better daily medicine. ❖

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