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Alpha-Lipoic Acid for the Prevention and Treatment of Diabetic Neuropathy

By Robert J. Nardino, MD

CAN THE KREBS CYCLE BE USED TO PRACTICE MEDICINE? THE search for agents that can impact the incidence of complications irrespective of blood glucose level continues. Alpha-lipoic acid (ALA), also known as thioctic acid, is a cofactor of the pyruvate dehydrogenase enzyme complex in the energy-producing Krebs cycle. Studied most thoroughly in Germany, ALA is used there to prevent and treat diabetic neuropathy.

Disease Course

In the Diabetes Control and Complications Trial, intensive hypoglycemic therapy resulted in a 64% relative reduction in the incidence of clinical diabetic neuropathy.[1] Although tight glycemic control is the standard for prevention of this complication, it is difficult to achieve in many patients. Diabetic neuropathy manifests as sensory loss of the distal extremities, painful neuropathy, or autonomic neuropathy with gastroparesis, orthostasis, and neurogenic bladder. Distal neuropathy often leads to foot ulcers, which result in increased morbidity (for example, amputation) and are associated with increased mortality. Amitriptyline is the standard for treatment of painful neuropathy symptoms. Gabapentin has been shown to be similar in efficacy to amitriptyline.[2] Aldose-reductase inhibitors, despite extensive research, have been disappointing in the treatment of diabetic neuropathy.

Biochemistry

In the mitochondria, blood glucose is converted to pyruvate during glycolysis. ALA is manufactured in the mitochondria and is a cofactor in the pyruvate dehydrogenase complex, which converts pyruvate into acetyl-CoA. The reduced form of ALA is the active form, and it acts as a hydrogen donor for other enzymes in the complex. Two lipoic acid groups also are attached to a lysine residue of dihydrolipoyl transacetylase, the core enzyme of the pyruvate dehydrogenase complex.

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INSIDE

Pharmacology

ALA is both water- and lipid-soluble. The only available study on the pharmacokinetics of ALA was conducted on 12 healthy volunteers and compared 200 mg or 600 mg oral doses with a 200 mg intravenous dose.[3] There was no difference in the plasma clearance (half-life) between the two oral doses.

Pathogenesis

Recent research has defined the role of oxidative stress, resulting from increased free radical activity, in the pathogenesis of diabetic neuropathy. This has been demonstrated in diabetic rats, in which oxidative stress led to delayed nerve conduction velocities.[4] It appears that neural hypoxia from an impaired microvascular supply is the insult that contributes to nerve damage; in addition, in rats with experimental diabetic neuropathy, nerve glucose uptake is reduced. A variety of antioxidants can prevent this reduced blood flow in experimental models.

Mechanism of Action

ALA acts as an antioxidant and increases cellular glutathione levels. It may also improve glucose utilization.

In diabetic patients with poor glycemic control and albuminuria, administration of ALA reduced biochemical markers of oxidative stress (plasma lipid hydroperoxides).[5] In 10 patients with diabetes and neuropathy, ALA therapy led to improvement in the microcirculatory response and to (desired) cooling of the extremity.[6] In animal models, parenteral ALA resulted in enhanced glucose transport and utilization.[7,8]

Early studies with low-dose ALA supplementation in humans resulted in increased levels of pyruvate and lactate, suggesting that the pyruvate dehydrogenase enzyme complex was being inhibited. However, this was subsequently overcome by the use of higher doses. ALA treatment resulted in an improved response to glucose loading in a small sample of lean and obese diabetic patients.[9,10] However, the effect on fasting blood sugar was very small.

Relevant Animal Studies

The reduction in nerve glucose uptake in experimental diabetic neuropathy can be reversed in a dose-dependent fashion with ALA administration, and this reduction is accompanied by improved neural function.[11] ALA supplementation also prevented reperfusion injury of peripheral nerves in an animal model.[12]

Clinical Studies

Ziegler et al reviewed the studies of ALA and diabetic neuropathy.[13] Fifteen clinical trials have been completed with a variety of patient populations, treatment protocols, and outcome measures. Studies using less than 600 mg/d ALA showed no clinical or physiologic benefit. Studies using more than 600 mg/d ALA did show some evidence of reduced symptoms and improved nerve function as based on neuroelectrophysiology. However, most of the studies have been small, and the benefits modest.

The major clinical studies have been conducted in Germany by Ziegler's group. In the ALA in Diabetic Neuropathy trial (ALADIN), 328 patients with type 2 diabetes mellitus and symptomatic neuropathy were randomized to treatment with 1,200 mg, 600 mg, or 100 mg parenteral ALA or placebo.[14] At three weeks, the 600 mg and 1,200 mg groups showed improvement over placebo in symptoms.

ALADIN II added an oral treatment phase.[15] Sixty-five type 1 and 2 diabetics with symptomatic polyneuropathy were randomized to 600 mg or 1,200 mg intravenous ALA or placebo, for five days, followed by oral ALA for two years. Endpoints were Neuropathy Disability Score (no change), and nerve conduction velocities (significant improvement).

ALADIN III, the largest study to date, was a multicenter, randomized, double-blind, placebo-controlled trial.[16] In this trial, 509 patients with type 2 diabetes and

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Alternative therapies popular among diabetic patients

A CANADIAN STUDY RECENTLY FOUND THAT 30% OF ALL diabetic patients regularly supplement their diabetes medications with alternative therapies—a finding that parallels the boom in alternative medicine's popularity as a whole. Although patients are willing to look beyond traditional treatments for their disease, scientific research is still trying to separate the real help from hype.

Diabetics appear to have significantly lower levels of antioxidants in their bodies than normoglycemics. Antioxidant supplements may be an answer, but the search is on now to find the proof. Some researchers say they are close to linking alpha-lipoic acid (ALA) with preventing nerve damage in diabetic patients.

Lester Packer, PhD, is a professor of physics and molecular and cellular biology at the University of California in Berkeley. In rat studies, Packer found that ALA supplementation brought measurable free ALA to the nerve cells, preventing or slowing nerve damage by up to 70%. He also found that the higher the dosage of ALA, the higher the amount of the antioxidant retained in the nerves.

Packer says he suspects that ALA may be instrumental in preventing the onset of diabetes since it helps improve the glucose utilization by muscle cells.

"If oxidative stress is a significant factor in diabetic complications, then antioxidant therapy is a logical candidate for preventing or ameliorating those complications," Packer says.

ALA is found in tiny amounts in potatoes, spinach, and red meat. To get 50 mg per day, one would have to consume 300 pounds of spinach. ■

evidence of symptomatic symmetric distal neuropathy were randomly assigned to 600 mg ALA given intravenously for three weeks or placebo, followed by 600 mg given orally tid for six months or placebo.

There were two outcome measures: Total Symptom Score and Neuropathy Impairment Score. The Total Symptom Score was based on the presence of pain, burning, and numbness in the feet. The Total Symptom Score decreased after three weeks with ALA therapy, but was no different than placebo when the study concluded after seven months. The Neuropathy Impairment Score was based on motor function, stretch reflexes, and sensation (vibration, proprioception, pinprick, and touch-pressure). This score was improved in the ALA group at both three weeks and seven months. A major limitation was that 25% of the patients dropped out of the trial.

All of the preceding studies included parenteral therapy. Only one small three-week study used only oral therapy.[17]

In the Deutsche Kardiale Autonome Neuropathie study (DEKAN), 73 patients with cardiac autonomic neuropathy as measured by heart rate variability were treated with 800 mg/d ALA or placebo.[18] There was a small increase in heart rate variability but no change in symptoms. Again, a large number of patients dropped out of the trial (17 of 73), limiting the ability to detect a clinically meaningful difference.

Lack of effectiveness, intercurrent disease, and noncompliance were reasons cited for the high dropout rates in these studies. The effects of ALA occurred without lowering of the blood sugar.

Adverse Effects

In both the ALADIN and DEKAN studies, no significant adverse effects were reported. In the ALADIN study, adverse events were equivalent in the treatment and placebo groups. Others have reported skin rash. Because of improved insulin sensitivity, there is a theoretical risk of hypoglycemia, but the clinical importance of this side effect is unknown. ALA may interfere with thiamine utilization. There are no data available concerning the use of ALA in pregnancy or lactation, and its use in these settings should be avoided.

Drug Interactions

No drug interactions with ALA have been described. The glucose-lowering effect of ALA in clinical trials was modest, and adjustment of insulin or oral hypoglycemic drugs should be based on the results of home glucose monitoring.

Other Effects

The first clinical use of ALA in humans was to treat a variety of liver diseases, including ethanol-induced damage, mushroom poisoning, and carbon tetrachloride toxicity. ALA was found to be effective at inhibiting replication of HIV-1 in cultured T lymphocytes.[19] It also is being investigated as a means to mitigate the toxic effect of certain chemotherapeutic agents.

ALA is used by some diabetic patients to lower blood glucose levels. It is approved as a drug in Germany for

Table 1

Price comparisons of alpha-lipoic acid

Manufacturer	Formulation	Price/Quantity
Carlson Laboratories	300 mg	$22.50/30 tablets
Source Naturals, Inc.	200 mg	$27.60/60 tablets
Solgar Co.	200 mg	$26.50/50 vegicaps
Twinlab, Inc.	100 mg	$21.95/60 capsules
Country Life	100 mg	$18.95/50 capsules
The Vitamin Shoppe	100 mg	$31.95/120 tablets
Natrol, Inc.	100 mg	$29.95/100 capsules
Kal	100 mg	$27.58/60 tablets

Source: Online mail-order firms

the treatment of diabetic neuropathy, and the recommendation is parenteral treatment for three weeks followed by oral therapy, as in the ALADIN III trial.

Formulation

ALA can be found in foods that contain mitochondria in large amounts. The best dietary source is probably red meat, the ingestion of which many patients are now limiting. Investigations are underway to determine the amount contained in plant foods.

Most supplements contain doses in the 50-100 mg range, but some contain higher doses to more easily approach the doses used in clinical trials. (*See Table 1 for price comparison of ALA supplements.*)

Conclusion

ALA has demonstrated antioxidant properties, and increasing evidence implicates oxidative stress in the etiology of diabetic neuropathy. Randomized clinical trials, conducted primarily in Germany, have demonstrated some improvement in nerve function, and to a lesser extent, symptoms in diabetic patients with peripheral neuropathy.

However, these studies have suffered from high dropout rates, and there are no studies specifically addressing neuropathy prevention in patients who have not yet developed it. Preventive effects are inferred by slowing the progression of established neuropathy. In addition, it is not clear whether oral dosing alone will be effective, as the largest studies have been performed primarily with parenteral therapy, though one study demonstrated no significant difference in plasma half-life between oral and intravenous doses.[3]

A large multicenter trial in North America and Europe investigating oral ALA and its effect on slowing the progression of diabetic neuropathy has been initiated. Another area of investigation is the combination of ALA and gamma-linoleic acid. The ultimate test of efficacy would be a decrease in neuropathy-related morbidity, such as infection, amputation, and mortality.

Recommendation

Patients with type 1 or 2 diabetes with symptomatic peripheral neuropathy may benefit from ALA therapy. The current best evidence supports intravenous therapy for three weeks followed by oral doses; however, intravenous therapy is not available in the United States. It is unclear whether oral therapy alone leads to the same benefit. Patients deciding to try this treatment should take 600 mg/d. Because ALA may lower blood sugar levels, blood glucose monitoring should be done more frequently after initiating ALA therapy. Further research is necessary to determine if patients without neuropathy should use ALA to prevent its development. ❖

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Can Stinging Nettles Take the Sting out of Hay Fever?

By Dónal P. O'Mathúna, PhD

THE STINGING NETTLE, THAT DISTINCTIVE DARK GREEN, hairy plant found in wastelands the world over, has brought many children to tears and adults to swearing. In fact, the term *urticaria* is derived from nettle's official name, *Urtica dioica*, and describes the type of rash produced by nettles. Paradoxically, in the United States, nettle has developed a reputation for the relief of hay fever symptoms (allergic rhinitis). Anything mild and effective that relieves the irritating symptoms of hay fever would be widely welcomed.

Background

A medicinal and culinary plant, stinging nettle has been used around the world to treat asthma, allergies, coughs, rheumatism, and the symptoms of benign prostatic hyperplasia (BPH). It has been given as a diuretic and an antispasmodic.[1] Both nettle root and the above-ground parts are used, although their constituents are somewhat different. During the 19th century, the principle of similarity (think bushy prongs) led to widespread use of nettle juice to stimulate hair growth and to the traditional recommendation that paralyzed limbs be whipped with nettles.[2] Nettles remain a staple vegetable in certain countries and are commonly incorporated into soups. Young nettle shoots are nutritious and contain as much carotene and vitamin C as spinach and other greens.[1]

Pharmacology

The nettle hair is a capillary with a bladder at the base and a tiny bulb at the tip.[3] When the bulb is broken off by contact, a fine needle-like structure is exposed which penetrates the skin and injects a fluid. This fluid's composition is not completely established, but it contains acetylcholine, histamine, and serotonin (5-hydroxytryptamine).[4] Nettle stings are more severe and long-lasting

than those induced by synthetic mixtures of these compounds, leading to suspicion that the sting also contains a potent histamine-releasing compound.

Nettles contain a wide variety of other compounds, including formic acid, β-sitosterol and other sterols, coumarin (scopoletin), flavonoids, carbohydrates, amino acids, and a relatively high amount (2.7%) of chlorophyll.[5] The root also contains a lectin (a large sugar-protein compound) called Urtica Dioica Agglutinin (UDA) which has been shown to inhibit prostaglandin and leukotriene synthesis.[6] UDA and β-sitosterol are believed to underlie nettle's use for rheumatism and BPH. Other active ingredients in nettle have not been identified, and a mechanism of action for nettle in hay fever is not known.

Clinical Studies

In Germany, several observational studies and two randomized, double-blind studies support the use of nettle root as a diuretic and for symptomatic relief of mild BPH.[7] But searches of MEDLINE, International Pharmaceutical Abstracts, Toxline, and The Cochrane Library (using nettle and urtica) produced only one clinical trial using nettle to treat hay fever.[8]

Volunteers were sought in Oregon during hay fever season (May through early July). Subjects were required to have at least moderately severe symptoms in two of the following three categories: rhinorrhea, sinus congestion, and excessive lacrimation. The study accepted 98 subjects who were randomly assigned to receive capsules containing either placebo or 300 mg freeze-dried *Urtica dioica* in a preparation containing primarily leaves and stems. According to a conversation with P. Mittman (June 2000), a random number list was used for group assignment, and both patients and researcher were blinded. Subjects were asked if they thought they received placebo, but their answers were not published.

Subjects were instructed to take two capsules upon onset of hay fever symptoms; within one hour subjects were told to evaluate and record their responses as either dramatic improvement, moderate improvement, no change, or worse. Subjects answered other general questions at the end of the trial, the duration of which was not reported.

Of the 98 participants, 69 finished the study, 31 taking nettle and 38 on placebo. Twenty were lost to follow-up, seven took fewer than five doses and felt unable to evaluate their product, and two withdrew because of side effects. The 69 subjects took between five and 34 doses, or an average of 17.8 doses, during the trial period. The average daily dose was 2.8, with a range of 1 to 7. It was not stated if a "dose" was 1 or 2 capsules.

The percentage of people in the nettle group who reported at least one instance of each type of symptom change were: dramatic improvement (32%), moderate improvement (84%), no change (74%), or worse (32%). For those taking placebo, the results were: dramatic improvement (16%), moderate improvement (71%), no change (84%), or worse (36%).

Participants were asked to make an overall assessment of their product. Of those taking nettle, 13 (42%) rated it as ineffective and 18 (58%) as moderately or highly effective. For the placebo, 24 (63%) rated it as ineffective and 14 (37%) as moderately or highly effective. When asked to compare the product with previous hay fever medicines used, of those taking nettle, 16 (52%) rated it as less effective and 15 (48%) as the same or more effective. For the placebo, 30 (79%) rated it as less effective and 8 (21%) as the same or more effective. Statistical analysis of the results was not published, but according to a conversation with P. Mittman (June 2000), chi-squared tests showed that the differences between nettle and placebo were statistically significant ($P < 0.05$).

Adverse Effects

In the above study, seven people taking nettle and five taking placebo reported mild gastric discomfort when taking the capsules on an empty stomach.[8] Two people withdrew because the nettle intensified their allergy symptoms. A study of nettle extract for BPH reported side effects in less than 1% of 4,087 patients.[7] The most common effects were gastrointestinal complaints and skin allergies. Nettle has a folk use as an abortifacient, and uterine contractions have been observed in animal studies.[9] For this reason, women who are or who want to be pregnant should not use nettle products.

Drug Interactions

The diuretic effect of nettle is well established; thus, it may interfere with other diuretics and heart failure medications. The presence of coumarin and the many other compounds suggests an interaction with anticoagulant therapy is likely. Animal studies have documented CNS-depressant activity for nettle, which may potentiate other drugs with these effects.[9] Anecdotal reports of nettle have shown both hypoglycemic and hyperglycemic activity, making its use by diabetic patients unwise.

Formulation

Nettle is available in capsules, as a dried leaf and root extract, or as a tincture. Nettle products are recommended for use as needed, with no limit suggested. A tea can be

made from the dried herb, with 2-4 g used three times daily for medicinal effects. Teas, however, are notorious for their imprecise drug-delivery dosages.

Regulation

In Germany, an alcohol extract of nettle root is approved as a drug for use as a diuretic, especially for the symptomatic alleviation of BPH.

Conclusion

Stinging nettle has a long folk medicine reputation. It appears to be well tolerated, although allergic skin reactions can occur. Its use for the relief of hay fever symptoms is based on anecdotal evidence and one controlled study. Although well-designed, this study measured no objective outcomes, the dropout rate was 30%, and the study's report omitted many important details. The placebo group had similar results, even reporting similar numbers and types of side effects. However, 32% of the placebo group had mild hay fever symptoms initially, whereas only 10% of the nettle group had mild symptoms. This might have influenced the results, but without adequate power and other statistical analysis, the significance of the results is uncertain.

Recommendation

Can nettles compensate for all the tears they cause in the wild by drying up the secretions of hay fever sufferers? Probably not. But nettle products may offer some symptomatic relief for some people with hay fever. A one-week trial like that in the study reported here may be appropriate, especially in otherwise healthy patients who are not and who do not want to be pregnant. However, the evidence suggests a trial with a placebo might be just as effective. Nettle seems to be well tolerated, although patients should watch for allergic reactions. For patients taking medications for other conditions, especially cardiac conditions, the potential for drug interactions outweighs the uncertain chance of benefit. ❖

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Mind-Body Medicine as Treatment for Female Infertility

A baby is an inestimable blessing and a bother.
Mark Twain,
letter to Annie Webster,
September 1, 1876

By V. Jane Kattapong, MD, MPH

Conceiving a baby can be a trial and a tribulation. In more than one quarter of infertile couples, no somatic cause can be determined.[1] It is not surprising then that when women find that they are unable to conceive, they feel stressed. Reproduction, after all, is a basic species-survival instinct.

Both global and relationship stress may result from infertility.[2] Women experiencing problems with fertility have a higher prevalence of negative feelings than women without fertility problems.[3] Social, sexual, and relationship themes are among the stressors typically perceived by women undergoing infertility treatments.[2] Since these stressors appear to weigh more heavily on

women than men,[2] stress reduction techniques designed for women being treated for infertility can provide a great service to these women.

Mechanism of Action

Does stress cause infertility, or does infertility cause stress? Although a relationship between the two has long been suspected, the causal role of one vis-à-vis the other remains unclear. In one case-control study of 22 infertile vs. 10 fertile couples, infertile couples were found to have higher mean anxiety scores based on the State Trait Anxiety Inventory, the Manifest Anxiety Scale, the Sixteen Personality Factor Test, and the Personality Questionnaire.[4] Limited work has suggested that being free from anxiety may be associated with conception, and that high levels of anxiety are associated with the absence of conception.[5]

Stress and infertility do appear to be associated, and each may fuel the other. In addition, ovulatory prolactin elevation may be a marker for stress. Prolactin "spikes" are thought to be associated with excessive emotional response. Elevated prolactin levels occurring intermittently mid-cycle may be associated with low secretory-phase progesterone concentrations and early luteal regression.[6] Prolactin levels, in some patients, may be a marker for stress-associated infertility.[7]

Finally, the physiologic effects of meditation have been studied since the 1970s by Harvard cardiologist Herbert Benson.[8] Benson has described the phenomenon that occurs after 20 minutes of relaxation: physiologic changes including decreases in oxygen consumption, carbon dioxide elimination, heart rate, respiratory rate, blood pressure, muscle tone, and arterial blood lactate.[8] Benson called this phenomenon "the relaxation response." Similar physiological responses have been described following hypnosis, progressive muscular relaxation, autogenic training, and meditation, and it is likely that these techniques are all methods for achieving the same relaxed state.[9] Whether the relaxation response constitutes a mechanism of action, or simply a means to an end, deserves further exploration.

Animal Studies of Stress and Infertility

Although relatively little is known about the relationship between stress and infertility in humans, the effects of stress on infertility in animals have been studied in the veterinary and zoological literature. In pigs, a variety of factors related to infertility, including social, environmental, and management influences, have been described.[10] Social factors such as crowding, repeated handling, and moving were thought to influence stress-related infertility in pigs. In ewes, transport occurring while the ewes were in the follicular phase of their menstrual cycle disrupted gonadotropin secretion, and was believed to have a negative impact on fertility.[11] Thus, in the animal literature, stress seems to be fairly well accepted as a cause of infertility.

Mind-Body Medical Techniques

Hypnosis. In a literature review and case series study,[12] 14 of 15 patients who participated in a hypnosis treatment program were able to conceive successfully. The case study, involving two cases, utilized hypnotic techniques including induction, information provision, and positive suggestion. The induction consisted of optical fixation, progressive relaxation, and numerical countdown to achieve the state of hypnosis. During the hypnotic state, guided imagery was provided to enable visualization of fallopian tube musculature relaxation. Post-hypnotic instruction was given to enable self-hypnosis at home. Gravitz's study was uncontrolled. (For more information on hypnosis and guided imagery, see *Alternative Medicine Alert*, March 2000, pp. 30-34, and June 1999, pp. 61-64.)

Autogenic therapy. Autogenic therapy consists of gentle exercises in body awareness and physical relaxation, progressively involving the limbs and viscera. The goal of autogenic training is to decrease stress responses and increase relaxation.[7] Autogenic training has been described as a technique that may lower psychological stress in women with unexplained fertility. It may also lower the biochemical stress marker, prolactin.[4]

Relaxation response. The relaxation response is reasonably conceptualized as the opposite of the fight-or-flight response, and has been adapted as a treatment modality for many somatic disorders that may have a psychosomatic component.[9] (For more information on the relaxation response, see *Alternative Medicine Alert*, February 1998, pp. 13-16.)

In one convenience study, 54 consecutively enrolled participants completed a behavioral treatment program.[5] All participants had an established diagnosis of infertility and had completed their infertility work-up. Most participants had a diagnosis of unexplained infertility; the mean duration of infertility was 3.3 years. Using a pre-test/post-test design, significant ($P < 0.05$) decreases were found in participants' scores on measures of depression, anxiety, and fatigue, as well as significant increases in vigor/activity. In addition, 18 (34%) of the participants became pregnant within six months of completing the program.

Though this study too was uncontrolled and limited

in enrollment, a relatively high rate of pregnancy occurred as a "side benefit" of the program's stated stress-reduction goals. Many participants reported dramatic improvements in feelings of self-esteem and self-empowerment.

Safety

No adverse effects of mind-body medicine, stress reduction, or autogenic training have been reported. Adverse effects for hypnosis have been reported, especially with individuals who have psychotic conditions as well as personality disorders.[14] We have previously recommended that these persons be treated only under the supervision of an experienced, licensed health care provider with expertise in the use and limitations of hypnosis in the setting of psychiatric disorders.[15]

Training for Clinicians

Several prominent centers offer training for clinicians. The Washington D.C.-based Center for Mind-Body Medicine, among others, offers a week-long course to help clinicians integrate mind-body-spirit medicine into practice. In addition the British Association for Autogenic Training and Therapy (BAATT), formed in 1984 to train therapists and maintain standards, offers a three-year professional training course.

In September 1987, the Mind/Body Program for Infertility was established at Beth Israel Deaconess Medical Center in Boston. This 10-week program for individuals with stress associated with any medical condition focuses on teaching these individuals to elicit the relaxation response.[13] (*See Table 1 for physiological correlates of elicitation of the relaxation response.*) Each session begins and ends with a group relaxation-response exercise that participants are expected to practice daily at home. Additional training is offered in stress management, physical exercise, nutrition, and group support.

A focus on infertility required modification of Benson's basic work. The infertility program limited the group size to 15, added a 30-minute sharing/support segment to the beginning of each of 10 sessions, invited husbands to attend two of the 10 sessions, had one of the sessions occupy an entire Sunday of yoga, exercise, and couples' cognitive-behavioral exercises, and devoted one additional session to developing self-empathy and compassion. Other session topics included:[5]

- Introduction to the physiology of stress, the relaxation response, and the relationship between stress and the reproductive system
- Diaphragmatic breathing and mini-relaxation response exercises
- Cognitive restructuring and affirmations (the confrontation and subsequent rethinking of recurrent negative thought patterns)
- Developing self-empathy and compassion
- Mindfulness (increased awareness of sensations and perceptions)

Table 1

Physiological correlates of elicitation of the relaxation response

- Decreased oxygen consumption
- Decreased carbon dioxide elimination
- Decreased heart rate
- Decreased respiratory rate
- Decreased blood pressure
- Decreased muscle tonus
- Decreased arterial blood lactate

Adapted from: Benson H. *The Relaxation Response*. New York: William Morrow; 1975.

Training for Patients

According to BAATT, typical autogenic training involves 8-10 weekly group sessions lasting approximately 90 minutes each. Patients learn a series of exercises to help them enter deep states of relaxation and experience relief from negative stress.

Conclusion

The relaxation response advocated by proponents of mind-body medicine may go by many different names: meditation, autogenic training, hypnosis, and more. Limited, mostly uncontrolled studies have suggested that regular elicitation of the relaxation response relieves stress associated with infertility and, in addition, improves pregnancy rates. Further well-designed, controlled studies will be necessary to establish the role of relaxation therapy modalities more conclusively. However, the utilization of mind-body medicine techniques to elicit the relaxation response appears to be a useful adjunct to more traditional forms of infertility treatment.

Recommendation

Regularly practicing to achieve the relaxation response may decrease anxiety and feelings of stress. It appears possible that a side-benefit of regularly eliciting the relaxation response is enhanced pregnancy rates in

women treated for infertility. No adverse effects of the relaxation response have been reported. Despite limited evidence, elicitation of the relaxation response can be recommended for women with infertility since it may provide benefit and does not appear to be harmful. ❖

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CME Questions

1. Factors in the pathogenesis of diabetic neuropathy include:

a. neural hypoxia.
b. microvascular damage from free radicals.
c. reduced glucose uptake by nerves.
d. All of the above

2. From clinical trials, the minimum effective dose of alpha-lipoic acid is:

a. 200 mg.
b. 600 mg.
c. 800 mg.
d. 1,200 mg.

3. The best evidence for a medicinal use of nettles exists for the relief of symptoms of:

a. hay fever.
b. rheumatism.
c. benign prostatic hyperplasia.

4. The potential for drug interactions with nettle seems highest with:

a. contraceptives.
b. diuretics.
c. insulin.
d. analgesics.

5. The relaxation response includes which changes in physiological parameters?

a. Decreased heart rate
b. Decreased respiratory rate
c. Decreased blood pressure
d. Decreased oxygen consumption
e. All of the above
f. a, b, and c

6. Women undergoing infertility treatment have been found to have:

a. higher prolactin levels than controls.
b. lower prolactin levels than controls.
c. the same prolactin levels as controls.

With Comments from John La Puma, MD, FACP

American Ginseng for Postprandial Glycemia

Source: Vuksan V, et al. American ginseng (*Panax quinquefolius* L.) reduces postprandial glycemia in nondiabetic subjects and subjects with type 2 diabetes *Arch Intern Med* 2000;160:1009-1013.

DESPITE A LACK OF MEDICAL EVIdence to support its therapeutic efficacy, the use of herbal medicine has increased considerably. Ginseng, one of the most widely used herbs, is hypothesized to play a role in carbohydrate metabolism and diabetes mellitus. We therefore undertook a preliminary short-term clinical study to assess whether American ginseng (*Panax quinquefolius* L.) affects postprandial glycemia in humans.

On four separate occasions, 10 nondiabetic subjects (mean [+/-SD] age, 34 +/-7 years; mean [+/-SD] body mass index [BMI], 25.6 +/-3 kg/m^2) and nine subjects with type 2 diabetes mellitus (mean [+/-SD] age, 62 +/-7 years; mean [+/-SD] BMI, 29 +/-5 kg/m^2; mean [+/-SD] glycosylated hemoglobin A_{1c}, 0.08 +/-0.005) were randomized to receive 3 g ginseng or placebo capsules, either 40 minutes before or together with a 25-g oral glucose challenge. The placebo capsules contained corn flour, in which the quantity of carbohydrate and appearance matched the ginseng capsules. A capillary blood sample was taken fasting and then at 15, 30, 45, 60, 90, and 120 (only for subjects with type 2 diabetes mellitus) minutes after the glucose challenge.

In nondiabetic subjects, no differences were found in postprandial glycemia between placebo and ginseng when administered together with the glucose challenge. When ginseng was taken 40 minutes before the glucose challenge, significant reductions were observed ($P < 0.05$). In subjects with type 2 diabetes mellitus, the same was true whether capsules were taken before or together with the glucose challenge ($P < 0.05$). Reductions in area under the glycemic curve were 18% +/-31% for nondiabetic subjects and 19% +/-22% and 22% +/-17% for subjects with type 2 diabetes mellitus administered before or together with the glucose challenge, respectively.

American ginseng attenuated postprandial glycemia in both study groups. To prevent unintended hypoglycemia, it may be important that nondiabetic subjects take American ginseng with the meal.

COMMENT

The seemingly paradoxical combo of ginseng inside sugary drinks, from new age beverages to evocative 2.3 ounce bottles sold in Asian markets, may have some basis in science. Maybe a little ginseng makes the sugar go down.

Usually prescribed as a tonic to relieve fatigue, boost energy, improve concentration, and increase work capacity, ginseng has been used for millennia, and is available in Germany by prescription, though not intended for diabetes.

With the explosion of type 2 diabetes (and parallel rise in obesity), something is needed to attenuate postprandial glycemia—especially hyperglycemia. These investigators capitalized on basic research to suggest just that effect, and in both controls and diabetics, postprandial glycemia was lessened when ginseng was taken before a glucose load, and in diabetics, also when taken with the glucose load.

American ginseng (*P. quinquefolius*) is reported to be milder than Asian ginseng (*P. ginseng*). Both contain ginsenosides, reportedly the active chemicals, especially ginsenoside Rb-1, which reportedly decreases islet cell insulin concentrations. Most of the adverse effects reported occur with Asian ginseng, not American ginseng, the wild variety of which is now an endangered species. Both American and Asian ginseng come in whole root, powders, tinctures, capsules, tablets, teas, and extracts. Ginseng's interaction with antiplatelet/anticoagulant drugs is increasingly well-known.

Many patients—especially those at risk for bleeding, pregnant, or hypertensive—will have contraindications to ginseng use. Nothing is known about long-term ginseng use for diabetes control, though others have found favorable effects of Asian ginseng on hemoglobin A_{1c} levels. This pilot study, like all good ones, raises more questions than it answers.

Recommendation

Suspect ginseng interaction with glipizide, glyburide, metformin, and the two glitazones remaining on the market—especially if blood sugars seem erratic. This pilot study is a good reason for better research on this subject. Included in the next trial should be a placebo arm and an arm for those who adhere to a weight-lowering, fitness-improving regimen. ❖

Permanent Magnets for Low Back Pain

Source: Collacott EA, et al. Bipolar permanent magnets for the treatment of chronic low back pain: A pilot study. *JAMA* 2000;283:1322-1325.

CHRONIC LOW BACK PAIN IS ONE OF the most prevalent and costly medical conditions in the United States. Permanent magnets have become a popular treatment for various musculoskeletal conditions, including low back pain, despite little scientific support for therapeutic benefit.

To compare the effectiveness of one type of therapeutic magnet, a bipolar permanent magnet, with a matching placebo device for patients with chronic low back pain, we conducted a randomized, double-blind, placebo-controlled, crossover pilot study from February 1998 to May 1999 in an ambulatory care physical medicine and rehabilitation clinic at a Veterans Affairs hospital.

The trial included 19 men and one woman with stable low back pain of 19 years' mean duration, with no past use of magnet therapy for low back pain. Twenty patients were determined to provide 80% power in the study at $P < 0.05$ to detect a difference of two points (the difference believed to be clinically significant) on a visual analog scale (VAS).

For each patient, real and sham bipolar permanent magnets were applied on alternate weeks for six hours per day, three days per week for one week, with a one-week washout period between the two treatment weeks.

We assessed pretreatment and posttreatment pain intensity on a VAS; sensory and affective components of pain on the Pain Rating Index (PRI) of the McGill Pain Questionnaire; and range of motion (ROM) measurements of the lumbosacral spine, compared by real vs. sham treatment.

Mean VAS scores declined by 0.49 (SD, 0.96) points for real magnet treatment and by 0.44 (SD, 1.4) points for sham treatment ($P = 0.90$). No statistically significant differences were noted in the effect between real and sham magnets with any of the other outcome measures (ROM, $P = 0.66$; PRI, $P = 0.55$).

We conclude that application of one variety of permanent magnet had no effect on our small group of subjects with chronic low back pain.

COMMENT

Magnets are everywhere—in belts, shoes, hair bands, and ace wraps. They have real attraction: they're inexpensive to make, have a lot of flexibility, and are as available as the nearest home refrigerator, or Sports Authority.

For all the money that's being spent and made on magnets, one would think that data would exist to prove their helpfulness. But alas, supportive data remain elusive, despite the NIH Center for Complementary and Alternative Medicine's grant to investigators at the University of Virginia to study magnet treatment for fibromyalgia. They will get no help from these data.

Of course, this is only a pilot study. But relatively few Americans use magnet therapy for low back pain, and *Consumer Reports* suggests that those who do are less happy with it than just about everything else, from prescription drugs to herbal supplements to chiropractic treatment.

Recommendation

Patients with low back pain attracted to magnets should save their money. Advise them to spend it on exercise: If exercise were a pill, it would be called penicillin. Weight management, chiropractic treatment, and physical therapy are the next best options. ❖

Bromelain for Ulcerative Colitis

Source: Kane S, Goldberg MJ. Use of bromelain for mild ulcerative colitis. *Ann Intern Med* 2000;132:680.

"A 67-YEAR-OLD WOMAN WITH A history of ulcerative colitis continued to have three to four bloody bowel movements per day despite adequate doses of sulfasalazine, mesalamine, and topical steroids. She discovered bromelain at a nutrition/herbal store after researching 'digestive aids' and anti-inflammatory drugs. Within a week of taking two tablets of bromelain at each meal, she was having one formed bowel movement per day without blood or urgency. Endoscopy performed at that time revealed healed mucosa.

The second patient is a 60-year-old woman with a history of left-sided disease; her symptoms continued despite azathioprine, 2 mg/kg of body weight, and topical mesalamine. She had heard about bromelain from a friend who used it for 'colonic health.' After she took several doses, her diarrhea improved. Endoscopy revealed quiescent disease affecting the splenic flexure."

COMMENT

Because ulcerative colitis is a difficult-to-treat chronic condition, and because the drugs used to do so often have adverse effects, an effective, benign supplement would be especially useful.

Bromelain is the proteolytic enzyme present in pineapple juice; other enzymes are present in other tropical fruit, especially papain, a mixture of proteolytic enzymes found in a species of a papaya.

Bromelain has been reported to be used in the treatment of infectious colitis, and in noninfectious cystitis and post-traumatic conditions of swelling and inflammation. The authors speculate that bromelain may act as a fibrinolytic agent, as heparin appears to do in ulcerative colitis as well. It is also suspected that bromelain causes the release of a kinin, stimulating prostaglandin E1 compounds. In theory, bromelain may also increase the risk of bleeding when taken with other anticoagulants and antiplatelet drugs.

Food as medicine will be seen more in the coming years, but less in whole food form than in capsules. Can you imagine Dole Pineapples becoming Dole UC Relief? Not a chance. But bromelain tabs right next to sulfasalazine on a formulary? Easily imaginable.

Recommendation

Case reports of bromelain effectiveness are not enough to prescribe it in addition to pharmaceuticals, but they are enough to stimulate a serious research trial, and these should. Except in patients on anticoagulant/antiplatelet drugs and those at risk for pregnancy, be open minded and careful about its use. ❖

In Future Issues:

Tai Chi for Prevention of Falls

Kudzu Extract for Alcoholism

Chondroitin for Arthritis