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Apitherapy: What's the Buzz? Bee Venom Therapy for Arthritis and Multiple Sclerosis

PART I OF A SERIES ON APITHERAPY

By Susan T. Marcolina, MD, FACP

HONEYBEES, *APIS MELLIFERA*, HAVE LONG BEEN APPRECIATED FOR more than just honey.

Bee venom, although widely accepted in this country for use in desensitization protocols for patients who have suffered life-threatening anaphylactic reactions to bee stings, has not been widely accepted for the treatment of other ailments. It has long been used in Europe and Asia for the treatment of arthritic conditions and, more recently, multiple sclerosis (MS), a chronic neurodegenerative disease that may have different disease presentations and clinical courses in given patients.[1]

Historical Use

The use of bee stings for the treatment of rheumatism and baldness was discussed in the Edwin Smith Surgical Papyrus, which dates from approximately 2000 BC and is an important archive of medical practices in the ancient Nile Valley.[2] Even Hippocrates used dried pulverized bees and bee stings in his practice of medicine.[3]

Formal scientific inquiry into bee-related clinical applications began with Terc, an Austrian physician in 1880, who was the first to use bee stings in his practice as therapy for rheumatoid arthritis and neuritis. Although he published several favorable reports about salutary effects in his patients, widespread use of this modality in European medical practice did not occur until the early 1900s.[4]

Chemical Constituents of Bee Venom

Table 1 outlines the major chemical constituents of bee venom and their effects.

Depending upon the trees and flowers available to the bees in a given geographic area, the chemical make-up of the bee venom, as

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well as any other hive product, may vary significantly, thus affecting its potency and subsequent medicinal effects.[5]

Possible Mechanisms of Action of Bee Venom

Whether whole bee venom or an individual constituent is responsible for a sting's ability to mitigate symptoms is the subject of controversy.

One mechanism by which bee venom has been postulated to suppress the induction of arthritis is via adrenocortical hormone release. Zurier et al demonstrated the ability of whole bee venom, but not its component melittin, apamin, or phospholipase A fractions, to block the onset of adjuvant arthritis in rats. Neither whole venom nor its constituents had any effect on established disease. The suppressive effects of the venom were reversed by adrenalectomy.[6]

Previous studies by Vick and Shipman and Vick and Mehlman showed that whole bee venom produced sustained rises of plasma cortisol in dogs and monkeys, whereas hypophysectomy prevented bee venom-induced adrenal stimulation in these animals.[7,8]

Chang et al, however, showed that the time course of adjuvant arthritis suppression by bee venom (0.5 mg/kg concentration) to be different than steroid use.[9] These authors theorized that bee venom directly suppressed immune cells responsible for arthritis initiation. They also demonstrated that the inhibitory effect of bee venom on arthritis initiation was greatest when it was administered simultaneously with (and into the same animal paw as) the adjuvant. This suggested a role for antigen competition in blocking arthritis onset.

Finally, Somerfield et al showed in in vitro studies that whole bee venom inhibited superoxide and hydrogen peroxide production from normal human polymorphonuclear leukocytes in a dose-dependent fashion with maximal effect at 1.5 microgram/cc.[10] The investigators were able to isolate melittin as the peptide constituent responsible for this action. On this basis, they postulated that whole bee venom may have an important role to play in the treatment of inflammatory tissue damage in rheumatic, cardiac, and central nervous system disease. However, the doses of venom required for anti-inflammatory effects would require patients to be exposed to a prohibitively large number of bee stings or the equivalent in venom dosage.[11]

Clinical Studies

Kroner et al performed an uncontrolled study of 100 patients ages 21-74 years with rheumatoid arthritis treated with intradermal injection of bee venom solution (Apicosan) into their most painful joints.[4] All were given a test dose of venom prior to therapy and excluded from the study if they had a reaction. Seventy-three showed definite improvement as judged by a decrease in sedimentation index and an alleviation of clinical symptoms. Seventeen of these patients remained symptom-free six months to a year after discontinuation of the treatments.

Subsequently, however, Hollander et al reported the first controlled trial of bee venom efficacy in 24 patients with rheumatoid arthritis.[12] These patients received the equivalent of 10-30 bee stings as intradermal injections per visit over an average of 18 sessions with sessions performed twice weekly. Controls were nine rheumatoid arthritis patients injected with a milk protein mixture. Improvement occurred in seven of 24 (29%) venom-injected patients and in three of nine (33%) milk protein-injected patients. The conclusion was that bee venom therapy (BVT) offered no significant improvement in patients with rheumatoid arthritis.

Hauser et al performed a study of the response of 73 patients diagnosed with either chronic progressive MS or relapsing-remitting MS to BVT.[13] Patients were diagnosed with MS on the basis of MRI imaging, clinical symptoms, and/or clinical evaluation by their referring neurologists/physicians. Patients with a positive test

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EDITORIAL GROUP HEAD: Lee Landenberger.
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Table 1

Major chemical constituents of bee venom and their effects[3]

Constituent	% of Venom	Effects
Melittin	40-60%	Anti-inflammatory; antibacterial; radioprotective; antifungal; lysosomal membrane-stabilizing protein
Mast cell degranulating protein	2%	Anti-inflammatory
Apamin	1%	Anti-inflammatory; beta-andrenergic
Adolapin	1%	Anti-inflammatory; analgesic
Phospholipase A	12%	Cell lysis, pain
Hyaluronidase	< 3%	Spreading factor; hydrolysis of connective tissue
Acid phosphatase	< 1%	Induces allergic reactions
Histamine	1%	Vasodilator, pruritic

dose to bee venom were excluded. Patients received a subdermal injection equivalent to one bee sting every other day for one week and dosages were increased each week by one shot per session until positive clinical effects plateaued. If a skin wheal developed that was larger than a silver dollar, patients were to halve the venom dose.

Tracking of improvement/disability was assessed every three months for 12 months using the Multiple Sclerosis Follow Up Questionnaire, the Related Observable Symptoms Scale Survey (ROSS), and patient ratings on the Karnofsky Performance Status Scale. Twenty-two of 73 patients were dropped from the study due to lack of follow-up, inability to handle the pain from BVT injections, or inability of caregivers to give the injections. At 12 months, the remaining 51 subjects perceived improvement in balance (34%), coordination (32%), fatigue (44%), and bowel control (31%). Sadly, the study lacked a control and objective methods of measuring improvement in perceived parameters and had small numbers of patients with a large drop-out rate.

Current Usage

Table 2 summarizes the products from bees and bee hives currently used medicinally.

Administration of Bee Venom

Although many flying insects have a venomous sting, it is the honeybee that has been domesticated and easiest to raise and, therefore, its venom has been the subject of much study. Bees produce approximately 0.1 mg dried venom per venom sac.[14]

The use of live bees as sting therapy for various conditions presents practical problems, which include finding a source of bees, and then storing and retrieving the bees for use as stingers. It is difficult to control the amount administered when venom from live bees is used for therapy.[14]

Formulation

Present day collecting technologies are based upon the use of a collector frame in the bottom of the hive, which contains wire grids from which electrical shocks are administered to the bee. When the bees receive the electrical shock they sting onto a glass sheet. The collected venom dries on the sheet to a gum like substance without loss of potency and is subsequently scraped and stored in a cool, dry place and used to produce solutions in an injection form.

Dilutions of 1:1,000 (3x), 1:1,000,000 (6x), and 1: 1, 000,000,000,000 (12x) are used in homeopathic products. Apitronic Services in Calgary, Canada, collects and processes whole, dried honeybee venom, which it provides to research institutes, chemical and pharmaceutical companies, physicians, and pharmacies.[1,3]

Adverse Reactions

For 0.5-2% of the population, a bee sting can trigger anaphylaxis with hypotension, respiratory collapse, and even death unless prompt medical attention with epinephrine and supportive care is instituted. Use of BVT in these patients is contraindicated except for desensitization protocols under the supervision of qualified medical professionals.

Side effects reported during BVT include localized itching, burning, swelling, and pain at the injection site. BVT is contraindicated during pregnancy as it is an abortifacient.[15]

Conclusion

There is no conclusive evidence in clinical studies that BVT is useful for the treatment of arthritis or multiple sclerosis at this time.

Table 2

Products of bees and beehives and their uses[3,16]

Product	Hive Use	Properties	Clinical Applications
Pollen	Primary protein/vitamin source	Nutritive	Food, allergy desensitization
Propolis	Resinous glue/sealant	Antibacterial	Antiseptic
Honey	Primary carbohydrate source	Nutritive, antibacterial, hygroscopic	Burn/wound healing, food
Beeswax	Protection	Structural support	Emulsifying agent (cosmetics), desensitization
Bee venom	Predator repellent	Anti-inflammatory, histamine release	Desensitization, inhibition of mast cell degranulation, superoxide production, leucocyte phagocytosis (in vitro)

Recommendation

Physicians should not recommend BVT to their patients suffering from arthritis or multiple sclerosis because there is no evidence from clinical studies to show benefit to balance the inconvenience of pain, swelling, and possible risk of anaphylaxis. BVT is contraindicated in pregnancy. ❖

Dr. Marcolina is a board-certified internist and geriatrician in Issaquah, WA.

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Green Tea for Weight Loss

By Jay Udani, MD, and Myles Spar, MD, MPH

THERE HAS BEEN GROWING INTEREST IN THE USE OF green tea and green tea extracts to promote weight loss. As concern with adverse effects from ephedra products grows, more and more consumers are looking for alternative natural supplements to assist with weight loss. Green tea may be the best alternative.

Obesity

Obesity is a significant health problem in the United States. According to the Surgeon General's Report on Overweight and Obesity, 61% of American adults were overweight in 1999;[1] even more recently, 33% of adult females and 28% of adult males in the United States were estimated to be obese. The annual revenue for the dieting industry is estimated to be more than $30 billion.[2]

Green Tea

Tea is second only to water as the world's most popular beverage. Such popularity of tea has been

demonstrated in Asia for millennia, and the demand for this important beverage has been growing in the West, as its health benefits, ranging from cancer prevention—with potential for the inhibition of angiogenesis—to cholesterol lowering, have become more widely known.

Preparation

All tea is picked from a leafy green shrub in the same family as Camellia plants (*Camellia sinensis*). Only the most tender new leaves are picked for tea. If black tea is made, the new leaves are allowed to ferment and cure, thus oxidizing. This process adds flavor to the tea, but it also allows chemicals in the leaves to break down some of the active chemicals in the tea, such as the polyphenols, which appear to be responsible for green tea's many health effects. Black tea, therefore, may lack many of the health benefits that will be discussed in relation to green tea.

Green tea is prepared by lightly steaming the leaves after picking. This steaming preserves the polyphenols and prevents fermentation, destroying the enzymes that would break down the active compounds in the leaf and cause them to oxidize, thus preserving the activity of the polyphenols.

Physiology

Chemically, green tea functions as an antioxidant because of its particular types of polyphenols, known as catechins, which are up to eight times more powerful as antioxidants than vitamin C, as measured by total radical scavenging activity.[3] Antioxidants promote health by repairing or preventing damage caused by chemicals that generate free radicals; green tea polyphenols have been shown to be antimutagenic in vitro.

Green tea extract has been shown to inhibit breast cancer cell proliferation in vitro and in mouse models, perhaps by inhibiting angiogenesis.

Other Health Effects

Traditional Chinese medicine uses green tea to facilitate digestion, stabilize body temperature, and enhance mental function. Ayurvedic medicine employs green tea as an astringent, stimulant, and diuretic.

In humans, epidemiologic studies have shown chemoprotective effects of green tea. One study in Japan showed that increased consumption of green tea was associated with a decreased risk of developing adenomatous polyps of the sigmoid colon. Green tea also has been shown to decrease cholesterol and triglyceride levels.[4] Green tea also may decrease the occurrence of thromboembolism by inhibiting platelet aggregation.[1]

Mechanism of Action

It has been shown in vitro that the catechins in green tea can inhibit an important enzyme, catechol-O-methyl transferase (COMT), which normally causes a decrease in the amount of thermogenesis within adipose tissue. Because COMT degrades norepinephrine, it is thought that by inhibiting the action of COMT, green tea catechins allow for a prolonged effect of norepinephrine on thermogenesis and fat metabolism.

Green tea extracts also have been shown to inhibit lipolysis. Lipolysis is the process by which dietary fats (triglycerides) are broken down by gastric and pancreatic lipases so that the resultant fatty acids can be absorbed in the small intestine. Inhibition of the breakdown of triglycerides prevents absorption of the fat, therefore, in theory, promoting less weight gain.

Laboratory Studies

Studies have investigated the ability of green tea and green tea extract to stimulate thermogenesis and to inhibit triglyceride metabolism. Because green tea contains caffeine and caffeine is known to promote thermogenesis, several studies have been carried out to show the effects of the green tea catechin polyphenols.

In one study done on brown fat cells in vitro, it was shown that the catechins in the green tea extract worked much more strongly than caffeine alone. In fact, synergistic work with caffeine was observed: Caffeine had a similar effect to the catechins in inducing thermogenesis.[5] The effect was equal to or greater than an ephedrine-caffeine combination.[6]

In vitro studies have demonstrated a dose-dependent inhibition of lipolysis through inhibition of the gastric and pancreatic lipases by green tea extract. When these studies were replicated in conditions more similar to the human body, the results were less striking.[7]

Clinical Studies

A group from the University of Geneva compared green tea extract (containing 1,500 mg extract with 270 mg epigallocatechin and 150 mg caffeine) vs. caffeine (150 mg) vs. placebo in a double-blind three-arm study among 10 healthy men.[8] The green tea extract group had a significant increase in energy expenditure and fat oxidation over both of the other two arms. The tea group did show somewhat greater inhibition of carbohydrate oxidation. This means that the extract helped increase fat metabolism, contributing to a higher energy expenditure, but caused a decrease in carbohydrate metabolism. The decreased metabolism of carbohydrates reduced the energy expenditure, but the net change was still in favor of increased energy expenditure. The extract used was

an alcohol extract of dried green leaves containing 8.35% caffeine and 24.7% catechins.

A French group performed a double-blind randomized study of green tea powder vs. placebo in 60 obese women.[9] The green tea group exhibited significantly greater weight loss and decrease in waist circumference at 15 and 30 days. The amount of catechins was not specified, but the formula used included 250 mg whole tea powder in the form of green tea "Arkocaps." No side effects were mentioned when subjects were asked by investigators; no withdrawals or drop-outs were reported.

A more recent study was published using a newer version of the same formulation.[10] The green tea extract used was AR25, which contains 25% catechins. This study referenced older work showing that the extract inhibited gastric and pancreatic lipases and increased thermogenesis in vitro. This clinical trial showed a decrease in weight by 4.6% and waist circumference by 4.5% after three months of AR25 use.

Dosage/Formulation

The normal adult consumption of tea in Japan is 2-3 cups per day with an average of 60 mg of polyphenols per cup. Because green tea can seem bland to the American consumer used to the strong taste of black tea, marketers are producing green tea in a variety of flavors. These flavorings, if natural, appear to do nothing to decrease the health benefits of the tea and may make it easier for the average consumer to drink.

Despite the great increase in tea choices available, people will look for the increased convenience and stronger effects found in encapsulated forms. Available products usually are standardized to the total polyphenol content (60-97% total polyphenols) or to epigallocatechin gallate, the most powerful antioxidant in green tea. Decaffeinated products are recommended because in this form, green tea extract would provide a very high dose of caffeine. A dose of approximately 250 mg of polyphenols was used most often in clinical studies.

Adverse Effects

The polyphenols themselves in green tea have not been associated with any significant side effects or toxicity. There is evidence that condensed polyphenolic compounds in the form of flavonoids (catechins or tannins) of tea is linked to a high rate of esophageal cancer in regions of heavy tea consumption. A high tannin concentration in tea may be overcome by adding milk, which binds the tannin, possibly preventing its detrimental effects.[11] Other adverse effects that have been mentioned include gastrointestinal upset and constipation.[12] There also has been reported an association of microcytic anemia among infants with the intake of more than 250 mL/d.[13]

An average six-ounce cup of green tea will have from 10-60 mg of caffeine. Caffeine is a central nervous stimulant that can induce nervousness, insomnia, tachycardia, elevated blood sugar and cholesterol levels, and high levels of stomach acid and heartburn. Although this amount of caffeine is much less than is present in black tea or coffee, caffeine-sensitive individuals or those drinking a large amount of tea can see some of the negative effects of too much caffeine. These also could include jitteriness, tremor, and increased anxiety. For those people, a decaffeinated green tea is best.

Supplements containing concentrates of green tea that are not decaffeinated would contain large amounts of caffeine, which could lead to similar symptoms.

Conclusion

Although larger randomized controlled trials are needed, the few studies that have been done suggest that green tea may be a safe and effective alternative to ephedra for stimulating thermogenesis for weight loss. Further studies will require a longer evaluation of green tea to determine if the effect of green tea catechins is attenuated with time.

Preliminary in vitro and animal data also show promise for green tea's ability to inhibit lipolysis. Although this could be advantageous in terms of weight-loss promotion, it also could cause a decrease in the absorption of important omega-3 fatty acids and fat-soluble vitamins. Clinical trials in humans are needed for further clarification of green tea's role and its relationship to this mechanism of weight loss.

Recommendation

Decaffeinated green tea extracts have begun to demonstrate efficacy with minimal side effects; therefore, with more supporting research, this product could be useful as an adjunct to a weight-loss program. It is recommended that the consumer look for products listing the total polyphenol or catechin content. The clinical studies mentioned in this article used at least 250 mg of active catechins per day. Thus, it would be advisable to use an equivalent amount. Of course, the use of green tea or green tea extract must be incorporated into a more comprehensive weight-loss program that includes exercise and proper diet. ❖

Dr. Udani and Dr. Spar are Clinical Instructors, University of California Los Angeles School of Medicine; Dr. Udani also is Medical Director, Northridge Hospital Integrative Medicine Program, Northridge, CA.

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Testosterone and Andropause

By Dónal P. O'Mathúna, PhD

ALTERNATIVE MEDICINE ALWAYS HAS INCLUDED ITS share of anti-aging remedies. Supplements like DHEA, human growth hormone, melatonin, and other natural hormone therapies have been marketed as the elixir of youth. Testosterone is the latest addition to hormonal anti-aging remedies. Its use in older men has accompanied increased controversy over the existence of andropause, or male menopause, and if it exists, whether testosterone safely and effectively treats it. Given concerns about hormone replacement therapy in women, physicians likely will receive many questions about the safety of testosterone use from older male patients.

Background

Interest in the effects of testosterone in older men is traced to 1889 when a 72-year-old French physiologist, Charles Brown-Séquard, presented a medical paper on an extract prepared from dog and guinea pig testicles. Injecting the extract gave dramatically improved physical strength and cognitive abilities. However, a very recent experiment failed to produce physiologically significant quantities of testosterone in extracts prepared using Brown-Séquard methodology.[1] Nevertheless, testicular extracts were marketed widely until testosterone was identified in 1935 as the key male hormone.

As menopause results from reduced estrogen production, male symptoms that result from reduced testosterone levels have been labeled andropause, male menopause, viropause, male climacteric, or low-testosterone syndrome.[2] The necessity of injecting testosterone limited its popularity, until patches and gels became available.[3] The publicity has led to a doubling in the number of testosterone prescriptions between 1997 and 2001.[4]

Natural History and Pharmacology

Total testosterone levels decline gradually with age. At the same time, men report a variety of symptoms, which most commonly include a lack of energy, reduced muscle mass, loss of libido, erectile dysfunction, depression, and reduced cognitive function.

During menopause, estrogen levels decrease dramatically, but testosterone levels decline gradually in men, about 1% per year between ages 40 and 70.[2] This reduction occurs in free testosterone (the biologically active fraction); total testosterone usually does not decline until after age 60.[2] Individual variability is high, but testosterone production is estimated to be reduced by one-third at age 70 and by half at age 80.[5] The overall prevalence of actual hypogonadism is low, with estimates ranging from 20-30% of older men.[6] A common lower serum testosterone level on many assays is 350 ng/dL or 14 nmol/L.[7]

Testosterone levels are controlled by a complex interplay of several hormones, and are influenced by confounding factors, including smoking, obesity, alcohol

use, lifestyle, and concomitant illnesses. Some argue that the symptoms of andropause are due more to declining health with age, rather than declining testosterone levels. All the symptoms of andropause could be caused by other diseases and conditions, yet many are improved by supplemental testosterone.[8]

Mechanism of Action

Reduced testosterone production in older men originally was believed to be due to testicular dysfunction (primary hypogonadism), but now is believed to be related more commonly to hypothalamic-pituitary dysfunction (secondary hypogonadism).[5] Testosterone has powerful effects on libido and sexual arousal, and anabolic effects on muscle, bone, erythropoiesis, and the brain, affecting mood and cognition.[8]

Clinical Studies

Clinical studies have focused on the effects of testosterone replacement therapy on muscular strength and mass, sexual arousal, and general well-being. However, very few controlled studies exist, and those that have been conducted are small and of short duration. For example, 12 older men with serum testosterone levels less than 480 ng/dL were randomly assigned to receive biweekly injections of placebo or testosterone enanthate (doses adjusted to achieve normal physiological concentrations).[9] After six months, those receiving testosterone had significantly increased lean body mass, muscle mass, and muscle strength.

Another study enrolled 67 healthy older men (mean 76 years) with low bioavailable testosterone levels (< 4.44 nmol/L).[10] Subjects were assigned randomly to wear two 2.5 mg testosterone patches or placebo patches daily for one year. Only 44 subjects completed the study. Those using placebo patches suffered a 1.6% loss in femoral neck bone mineral density, while those using testosterone gained 0.3% ($P = 0.015$). The testosterone group had reduced body fat and increased lean body mass ($P = 0.001$). No significant differences were found in muscle strength, hematocrit, prostate-specific antigen (PSA), or signs of benign prostatic hyperplasia (BPH).

Very few controlled studies have examined sexual or cognitive changes with testosterone. A controlled study randomly assigned 227 hypogonadal men to either testosterone gel (either 50 or 100 mg/d) or testosterone patch (5 mg/d) for six months.[11] Sexual function and mood improved significantly in all groups after one month, with no further improvement. Lean body mass and muscle strength also improved, with the largest improvement in the 100 mg gel group ($P = 0.0002$). Hematocrit and PSA levels increased in all groups.

In an uncontrolled study, 10 hypogonadal men used testosterone gel for 12 weeks.[6] On average, total, LDL, and HDL cholesterol levels were each reduced 15% ($P < 0.005$), sexual arousal and spontaneous erections increased ($P < 0.02$), and mood and cognitive abilities improved ($P < 0.05$). In another uncontrolled study, five hypogonadal men (mean 277 ng/dL) with major depression refractory to selective serotonin reuptake inhibitor therapy received testosterone enanthate injections (400 mg biweekly) for 14 weeks. Four then received placebo injections. While taking testosterone, HAM-D depression scores dropped from 19.2 to 7.2 ($P = 0.01$). Within two weeks of placebo treatment, three subjects relapsed to a mean HAM-D score of 11.3 ($P < 0.05$).

Adverse Effects

The prostate is dependent on testosterone, but paradoxically, as testosterone levels drop with age, the prostate enlarges, leading to BPH in many older men,[12] and the discomfort of urinary symptoms. The single largest concern with testosterone administration is its impact on the prostate. Existing prostate cancer is an absolute contraindication for testosterone administration.[13] However, testosterone's role in causing prostate cancer is less clear. Controlled studies have found high serum testosterone levels associated with a higher risk of prostate cancer; others have found no correlation; still others have found reduced risk.[13] Testosterone administration in hypogonadal men can increase prostate volume and PSA levels, but within normal ranges. Some studies found that supplemental testosterone reduced prostate volume and PSA levels.[12] Careful prostate monitoring is essential when administering testosterone.

Patients with several other conditions should be monitored carefully when taking testosterone.[13] Those with liver disease should be cautious since the liver metabolizes testosterone, and high doses of testosterone can slow the liver's metabolism and increase the risk of toxicity. Serum lipid profiles are affected by testosterone, requiring monitoring of those with cardiovascular diseases. Hematocrit changes may progress to polycythemia. In rare cases, testosterone may lead to gynecomastia and thus is contraindicated in men with breast cancer. Testicular atrophy and decreased spermatogenesis also have been reported with use.

Formulation

Testosterone is available in various formulations.[8] Intramuscular injections use testosterone cypionate or testosterone enanthate (200 mg biweekly). These injections are uncomfortable and lead to wide swings in physiological levels. Oral testosterone undecanoate

(usually 160 mg/d) is better tolerated, but its absorption is highly variable. Testosterone patches better mimic physiological production, but have practical problems. Between 42% and 84% of users report adverse skin reactions, and are uncomfortable wearing the patch, especially when it is applied to the scrotum.[6] Topically applied gels are available either commercially, though their potency is generally low, or through compounding pharmacies.[6] Testosterone propionate is available as a generic preparation for topical application.

Ongoing Research

In June 2002 the National Institutes of Health and the Department of Veterans Affairs decided not to proceed with a large randomized controlled trial of testosterone replacement therapy, citing problems with designing a large enough study without subjecting many subjects to unknown risks.[4]

Conclusion

A growing number of symptoms associated with aging in men have been correlated with decreased levels of testosterone. Administration of testosterone, by injection, orally, or topically, reverses many of these symptoms. However, much remains to be learned about andropause and testosterone replacement. Great individuality exists among men in their production of testosterone and response to testosterone replacement. Normal ranges are broad, and laboratory tests vary widely. Most of the studies have, to date, been relatively small and of short duration, although one study found testosterone patches safe and well tolerated for 7-10 years.[14]

Although much remains to be learned about testosterone supplementation for the symptoms of andropause and reduced testosterone levels, studies to date have not revealed serious problems. PSA and hematocrit usually are increased, but their clinical significance remains unclear. The potential for testosterone to stimulate pre-existing but undetected prostate cancer is of greatest concern. In announcing a thorough review of testosterone replacement therapy, the National Institute on Aging and the Institute of Medicine cautioned that "testosterone supplementation remains a scientifically unproven method for preventing or relieving any physical and psychological changes that men with normal testosterone levels may experience."[15]

Recommendation

Clinicians are left in a difficult position, given the negative results of the Prempro trial last year, and the effectiveness of those hormones in controlling symptoms and (it was believed) in preventing cardiac disease. Men eager to find relief from their age-related symptoms already are asking clinicians hard-to-answer questions about testosterone replacement.

Men who have low testosterone levels may benefit from testosterone replacements with each formulation having its pros and cons. While using testosterone, patients should have their prostate and hematocrit closely monitored. Patients with prostate or breast cancer, and patients at high risk for either, should not be given testosterone.

Because most men's testosterone levels remain within the normal range, the risk-benefit analysis for them is less clear. Since many age-related symptoms can have several origins, other potential causes should be explored before prescription. ❖

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

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CME Questions

Effective with this issue, *Alternative Medicine Alert* is changing its testing procedure. You will no longer need to return a Scantron answer sheet to earn credit for this activity. Please review the text, answer the following questions, check your answers against the answer key, and then review the materials again regarding any questions answered incorrectly. To receive credit for this activity, you must return the CME evaluation in the envelopes enclosed with the June and December issues. For further information, refer to the "CME Instructions" below.

This testing procedure has proven to be an effective learning tool for adults. If you have any questions about the new testing method, please contact Customer Service at 1-800-688-2421.

CME Instructions: Physicians participate in this continuing medical education program by reading the article, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material. After completing this activity, you must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a certificate of completion. When your evaluation is received, a certificate will be mailed to you.

9. Bee venom therapy (BVT) is contraindicated in pregnancy.
a. True
b. False

10. Adverse effects due to BVT may include:
a. swelling.
b. pain.
c. systemic anaphylaxis.
d. pruritus.
e. All of the above

11. BVT is a useful treatment in which of the following circumstances?
a. Pregnancy
b. Chronic rheumatoid arthritis
c. Relapsing-remitting multiple sclerosis
d. Venom desensitization protocols for bee venom anaphylaxis

12. The polyphenols in tea stay active and are used for weight loss in which of the following teas:
a. black tea.
b. green tea.
c. oolong tea.

13. Green tea extracts taken for weight loss should contain the equivalent of approximately how many cups of green tea?
a. 1-2 cups/d
b. 3-4 cups/d
c. 5-6 cups/d

14. Testosterone replacement therapy is definitely contraindicated in patients with:
a. benign prostatic hyperplasia.
b. prostate cancer.
c. high blood pressure.
d. diabetes.

Answer key: 9. a; 10. e; 11. d; 12. b; 13. b; 14. b.

Clinical Briefs

With Comments from John La Puma, MD, FACP

Dietary Strategies for CHD Prevention

Source: Hu FB, Willett WC. Optimal diets for prevention of coronary heart disease. *JAMA* 2002;288:2569-2578.

A REVIEW WAS UNDERTAKEN OF THE best metabolic, epidemiologic, and clinical trial evidence regarding diet and coronary heart disease (CHD) prevention. Controlled trials with clinical endpoints were sought; as few exist, substantial weight was given to large prospective cohort studies that reported disease outcomes and metabolic studies with established intermediate endpoints.

Analyzing MEDLINE through May 2002 for epidemiologic and clinical investigations of CHD and major dietary factors (fat, cholesterol, omega-

3 fatty acids, trans-fatty acids, carbohydrates, glycemic index, fiber, folate, specific foods, and dietary patterns) yielded 147 original investigations and reviews of metabolic studies, epidemiologic studies, and dietary intervention trials of diet and CHD. Data were examined for relevance and quality and extracted by one of the authors.

Compelling evidence from metabolic studies, prospective cohort studies, and clinical trials in the past several decades indicates that at least three dietary strategies are effective in preventing CHD: substitution of nonhydrogenated unsaturated fats for saturated and trans-fats; increased consumption of omega-3 fatty acids from fish, fish oil supplements, or plant sources; and consumption of a diet high in fruits, vegetables, nuts, and whole grains and low in refined grain products.

However, simply lowering the percentage of energy from total fat in the diet is unlikely to improve lipid profile or reduce CHD incidence. Many issues remain unsettled, including the optimal amounts of monounsaturated and polyunsaturated fats, the optimal balance between omega-3 and omega-6 polyunsaturated fats, the amount and sources of protein, and the effects of individual phytochemicals, antioxidant vitamins, and minerals.

Substantial evidence indicates that diets using nonhydrogenated unsaturated fats as the predominant form of dietary fat, whole grains as the main form of carbohydrates, an abundance of fruits and vegetables, and adequate omega-3 fatty acids can offer significant protection against CHD. Such diets, together with regular physical activity, avoidance of smoking, and maintenance of a healthy body weight, may prevent the majority of cardiovascular disease in Western populations.

COMMENT

More than any other question, patients ask me, "Is it OK if I eat (fish) (butter) (fast food)?" Of course, I love this—I'd much rather try to clear up the confusion in the office, by e-mail, or on the phone, then have to deal with the stroke, heart attack, hypertension, diabetes, or cancer that is down the road.

Drs. Hu and Willett have championed the traditional Mediterranean diet, finding that it is not total fat that matters in heart disease, but the kind of fat. This review allows them to show us the money—with extensive and authoritative references.

They find that a variety of diets can prevent heart disease, as long as they include foods with omega-3 fatty acids (fish, flax, walnuts, and purslane); low glycemic loads and lots of soluble fiber (barley, oats, and beans); folic acid (grains, cereals, and leafy greens); nuts (especially walnuts and almonds); small amounts of alcohol (< 5 g/d); and more fruits and vegetables (especially leafy greens, and specifically not potatoes).

The authors acknowledge the anatomical success of cardiologist Dean Ornish's very low-fat diet, exercise, stress management, and yoga program, which significantly reduced progression of atherosclerosis, but find it "unnecessarily rigid and difficult for most people to follow."

They show why the major source of protein should come from nuts, soybeans, legumes, poultry, and fish; the major source of fats should come from the same, and from vegetables, olives, and canola; and the major source of carbohydrates should come from whole, unrefined grains, fruits, and vegetables. Trans fats should be minimized or eliminated, as should saturated fats.

Recommendation

Patients who have coronary disease and want to halt its progression should eat this way. To help them maintain motivation (and a healthy weight) over the long term, they need one-on-one accountability, effective self-monitoring, and 150-300 minutes of exercise weekly. Recommend a physician or dietitian who specializes in this work if you cannot give it your time. ❖

Treatment and Management of Pediatric Obesity

Source: Barlow SE, et al. Treatment of child and adolescent obesity: Reports from pediatricians, pediatric nurse practitioners, and registered dietitians. *Pediatrics* 2002;110(1 Pt 2):229-235; Trowbridge FL, et al. Management of child and adolescent obesity: Study design and practitioner characteristics. *Pediatrics* 2002;110(1 Pt 2):205-209.

THE PRIMARY AIM OF THIS STUDY WAS to identify interventions used by pediatric health care providers in treatment of overweight children and adolescents to identify provider educational needs. A secondary aim was to examine the association of certain provider characteristics with recommended evaluation practices.

A random sample of pediatricians, pediatric nurse practitioners, and registered dietitians (RDs) received questionnaires about their diet, activity, and medication recommendations for overweight patients and about referrals to specialists and programs. Results were examined for adherence to published recommendations and for associations with certain respondent characteristics.

A total of 940 providers responded (response rate: 19-33%). The majority recommended "changes in eating patterns" and "limitations of specific foods." Half or more encouraged "low-fat diet" and "modest calorie restriction." Less than 15% used "very low-calorie diet." Fewer RDs recommended more restrictive diets. More than 60% of all groups followed recommended eating interventions for school-aged children and adolescents. More than 80% followed recommended physical activity interventions for all age groups.

In each group, about 5% sometimes recommended prescription medication and herbal remedies for adolescents. None recommended surgery. Two-thirds of pediatricians and pediatric nurse practitioners often referred to RDs. Approximately 20% referred to child/adolescent weight programs, but for 27-42%, these programs or pediatric obesity specialists were not available. No consistent associations between respondent characteristics and adherence to recommended interventions were identified.

The providers generally promoted healthy eating and activity with minimal

use of highly restrictive diets or medication to control weight.

COMMENT

Pediatric obesity is truly alarming. In the United Kingdom, for example, pediatric obesity has doubled in the last 20 years: 20% of 9-year-olds are overweight, and 10% are obese—almost as bad as in the United States.

Pediatric obesity is not about cosmetics, appearances, willpower, or morality. It's about calories in/calories out; it's about role modeling and family dynamics; and it's about medical consequences. Effective clinical practice is just developing, and the condition is one with which many clinicians feel ill-equipped.

Arguably, the "recommended eating and exercise interventions" that the authors cite are either ineffective or not implemented. Few referrals are made to specialists by dietitians, and the U.S. Department of Agriculture's flawed Food Pyramid is part of many schools' curricula. Clearly, change is needed.

One intervention that is effective is limiting TV viewing. It's not just that kids are sitting around. It's that every hour, an average of 10 food commercials—fun, bright, upbeat—offer fast food, soda, candy, and sugary breakfast cereal. And those high-calorie, low-nutrient foods often are just a few steps, or a cry to Mom, away.

Cost is one objection to eating better that often is raised by parents. Cost analyses show that the cost of a healthful diet in a family-based obesity treatment program is significantly less expensive at 12 months than at baseline (*J Am Dietetic Assoc* 2002;102:645-656). This research also shows that pediatric obesity programs that involve parents are the most effective. Unfortunately, parents often have their own personal, psychological, and physical problems with this dilemma.

Recommendation

Because there is no consensus about how to treat pediatric obesity, except as a family, and because it is difficult to treat, seek out a practitioner, program, or web site that can work one-on-one with parents and kids.

Limiting television to a maximum of two hours daily is an evidence-based behavioral start—one clinicians should recommend and parents should track. ❖

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Supplement to *Alternative Medicine Alert*
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ALTERNATIVE MEDICINE ALERT™
A Clinician's Evidence-Based Guide to Alternative Therapies

Natural Gains Against the Pain of Arthritis

THE VAST MAJORITY OF AMERICANS USING COMPLEMENTARY THERAPIES ARE THOSE SEEKING relief from some kind of pain: arthritis, chronic back pain, and musculoskeletal pain. Arthritis pain alone has driven more Americans to seek complementary and alternative medicine (CAM) therapies than any other single affliction. And although most patients using CAM therapies for arthritis employ them as a supplement to rather than a replacement for mainstream medical care, they tell researchers they do so because their medications do not provide complete relief. In many cases, the use of CAM therapies corresponds to the severity of the pain.

Glucosamine and Chondroitin

The use of glucosamine sulfate with or without chondroitin sulfate is far and away the most popular supplement for the treatment of osteoarthritis.

Glucosamine is extracted from the shells of crustaceans and chondroitin is prepared from cow trachea or shark cartilage. Glucosamine has been reported to inhibit cartilage breakdown and stimulate regeneration of cartilage after damage. Chondroitin has been reported to block the enzymes that degrade cartilage.

Both supplements have been used for many years in Germany and other parts of Europe, and although their effects on joint damage are still being debated, most medical experts agree that glucosamine works as an anti-inflammatory, reduces pain, and is safe.

The best evidence available to date is a large three-year Belgian study that suggests that glucosamine slows the progression of osteoarthritis.[1] A similar placebo-controlled trial is underway in the United States under the auspices of the National Institutes of Health (NIH) and will include chondroitin, glucosamine-chondroitin, and nonsteroidal anti-inflammatory (NSAID) arms.

The evidence in favor of chondroitin is less convincing and there have been no clinical trials published on the popular combination of the two supplements. It remains unclear whether patients get any additional benefits by taking glucosamine and chondroitin together.

The operative daily dose for the subjects of the Belgian study was 1,500 mg of glucosamine. It usually is divided into two or three doses—and it may take four to eight weeks for effects to become noticeable. Chondroitin usually is used in similar dosages. If neither has an effect within 12 weeks, patients usually are advised to discontinue use.

Because glucosamine may affect glucose metabolism, it is not recommended for patients with diabetes until further trials provide better information on its effects on blood glucose levels.

Massage

A 2001 survey shows that more than half of osteoarthritis sufferers use massage therapy.[2] And a recent University of Miami (Florida) study of children with rheumatoid arthritis showed that subjects with mild-to-moderate forms of the disease who were massaged for 15 minutes daily by their parents for 20 days experienced immediate lowering of anxiety and

stress as measured by cortisol levels, decreased pain, and increased joint mobility.[3]

The most effective massage techniques are stroking, called effleurage in traditional massage, and passive joint movement to increase mobility.

Patients can be taught simple self-massage techniques that can be very helpful, especially for arthritic conditions of the hands, wrists, and elbows.

Acupuncture and Acupressure

Acupuncture, an ancient Chinese treatment, and acupressure, its non-invasive cousin, have become widely accepted in the United States and for a variety of medical conditions.

Acupuncture treatments, as prescribed by traditional Chinese medicine, typically involve the insertion of hair-fine needles into the skin along defined tracts called meridians, where they help stimulate the flow of *qi* or *chi*, vital life energy.

Acupressure and shiatsu massage, a Japanese form of acupressure, use no needles, but stimulate the same meridians by applying pressure to certain points on the body. Qualified practitioners can teach patients acupressure techniques.

A Japanese animal study showed that electrically controlled acupuncture needles appear to delay the onset and reduce the severity of arthritis while reducing the collagen antibody levels. Researchers speculate that acupuncture may inhibit the production of endogenous interleukin-1 beta and prostaglandin by suppressing interleukin and COX-2 gene activations.[4]

After a 1998 Consensus Panel review of the available public data, the NIH concluded that acupuncture is a promising treatment for postoperative pain and for nausea and vomiting associated with chemotherapy. The NIH also approved the use of acupuncture as primary or adjunctive therapy for osteoarthritis, tennis elbow, fibromyalgia, myofascial pain, low back pain, and carpal tunnel syndrome.

Diet

Researchers have long believed that food sensitivities trigger the inflammation of rheumatoid arthritis and perhaps even exacerbate the symptoms of osteoarthritis.

Not all patients show food sensitivities, but for many, identifying food sensitivities can make an enormous difference. Some of these patients may have suffered with arthritis for years, never realizing that simple dietary changes might help.

The key is to put patients on a supervised elimination test for several days, eliminating suspect foods and then re-introducing them one at a time to identify specific triggers. The most common triggers, by far, are proteins in dairy products and eggs, followed by corn and peanuts.

The theory was tested by a Norwegian study published in the *Lancet* in 1991 in which common arthritis food triggers were eliminated. Joint stiffness, swelling, and tenderness decreased and grip strength improved. The average pain score dropped from over 5 on a 10-point scale to below 3. Most importantly, when patients were checked a year later, the benefits were still there.[5]

A vegetarian diet appears to benefit about 50% of patients, including those without specifically identified food triggers.

Vitamins

The jury is still out, but the Framingham Heart Study suggests that vitamins D supplementation may be helpful alleviate symptoms of osteoarthritis and prevent deterioration.[6]

Patients should be advised not to exceed 400 IU of vitamin D daily because higher dosages have been shown to be toxic.

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