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Androstenedione for Performance Enhancement: Hard-Hitting Hormone or Harmful Hype?

By Dónal P. O'Mathúna, PhD

MARK MCGWIRE BECAME A BASEBALL HERO IN 1998 WHEN HE broke Roger Maris' home run record. During the season, the hero announced that he used androstenedione (or "andro"), which sent sales skyrocketing.[1] McGwire put himself center stage in the debate over how natural an athlete's performance ought to be. Some sports physicians and professional athletes accepted McGwire's personal use of andro, but criticized him for not warning kids about its potential dangers.[2] In response to this criticism, McGwire announced in August 1999 that he stopped taking andro four months earlier.[3]

Performance enhancing drugs are widely used. More than one million Americans have taken anabolic-androgenic steroids (AAS). Adolescents comprise one quarter of the users.[4] After hearing the home run hero's prior endorsement and looking at his forearms, many young athletes faced difficult decisions. Family members, coaches, and team physicians need to know about andro's potentially dangerous lure for young athletes.

Background and History

Research in the 1930s showed androstenedione had effects like those of AAS.[5] A 1962 study showed dramatic but short-term increases in serum testosterone levels.[6] The former East German sports establishment conducted research which led to an androstenedione nasal spray.[7] Athletes allegedly used this spray immediately before competition, relying on the spray's short duration to avoid detection. After the fall of the Berlin Wall, this research was commercialized, resulting in a German patent for androstenedione.[8]

The 1990 Anabolic Steroids Control Act classified AAS as Schedule III controlled substances, making them more difficult to obtain.[9] Androstenedione occurs naturally in Mexican yams and Scotch white pine, allowing its unrestricted sale in the United States in accordance with the 1994 Dietary Supplement Health and Education Act (DSHEA).

Pharmacology

Androstenedione (*see Figure 1*) is produced in the adrenal glands and gonads as part of the complex network of steroid hormones, being interconverted to testosterone, estrone, estradiol, androsterone, and others.[4] Athletes seek the anabolic effects of AAS like androstenedione, including increased muscle mass, organ size, physical aggressiveness, and decreased body fat. Androgenic activity stimulates the development of exaggerated male characteristics, viewed by athletes as an undesirable side effect. Despite the best efforts of chemists, resulting in the synthesis of hundreds of AAS, all AAS retain some androgenic activity.[9] Androstenedione's direct anabolic-androgenic activity is weak.

Mechanism of Action

Androstenedione is promoted as a natural testosterone booster and legal "source" of testosterone. Increased testosterone levels lead to greater muscle mass and strength gains in athletes and non-athletes.[10,11] AAS also increase protein synthesis in skeletal muscle and inhibit the catabolic effects of vigorous exercise, allowing faster recovery from intense training.[4]

Clinical Studies

In one of two published studies of oral androstenedione, two women took 100 mg androstenedione and blood was drawn at 0, 30, 60, and 90 min.[6] One woman's 60-min testosterone level was 660% higher than baseline, and the other's was 433% higher. The levels at 90 min remained elevated, but lower than the 60-min levels.

The 1995 German patent for androstenedione nasal spray included the results of human trials, but gave no details about the studies or their subjects.[8] Fifteen minutes after taking androstenedione, total serum testosterone levels increased either 40-83% (after 50 mg orally), 111-237% (100 mg orally), or 34-97% (3.5-15 mg nasally). A 48-97% testosterone increase was reported three to four days after discontinuing the nasal spray; an elevated level remained for another six to seven days.

King et al reported the first randomized controlled trial of oral androstenedione and described two separate controlled studies. In the first, 10 healthy men (mean age, 23 years) were randomly assigned to either 100 mg androstenedione or placebo.[12] Blood taken every 30 min showed androstenedione levels were significantly elevated—175% over baseline at 60 min and 325-350% between 90 and 270 min ($P < 0.05$). At 360 min, levels had returned to their 60-min level. Serum levels of free and total testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH) remained unchanged.

In King's second study, 20 healthy men (ages 19-29 years) undertook an eight-week resistance training program, and were randomly assigned to androstenedione or placebo.[12] Tablets (100 mg androstenedione or placebo) were taken three times daily during weeks 1, 2, 4, 5, 7, and 8 to simulate "washing-out" (a common AAS practice that allegedly prevents tolerance and reduces risks). All subjects were supervised lifting weights for all major muscles three times weekly on nonconsecutive days. Resistance for each muscle was set at 80-85% of a one-repetition maximum (1-RM).

Data for one subject were excluded when blood tests revealed previously undiagnosed diabetes mellitus. Overall body composition, muscle strength, and muscle fiber analysis for all subjects were consistent with a successful conditioning program. However, no significant differences were found between the two groups. Those taking supplements had 100% higher serum androstenedione levels than baseline at weeks 2 and 5 ($P < 0.05$). At week 8, the level remained elevated, but not significantly ($P = 0.07$). No significant changes occurred in either free or total testosterone levels within either group during training. In summary, androstenedione supplementation neither increased serum testosterone concentrations nor enhanced the strength gains of resistance training.

Total cholesterol, LDL, VLDL, triglyceride, liver enzyme, total iron, hematocrit, and hemoglobin levels

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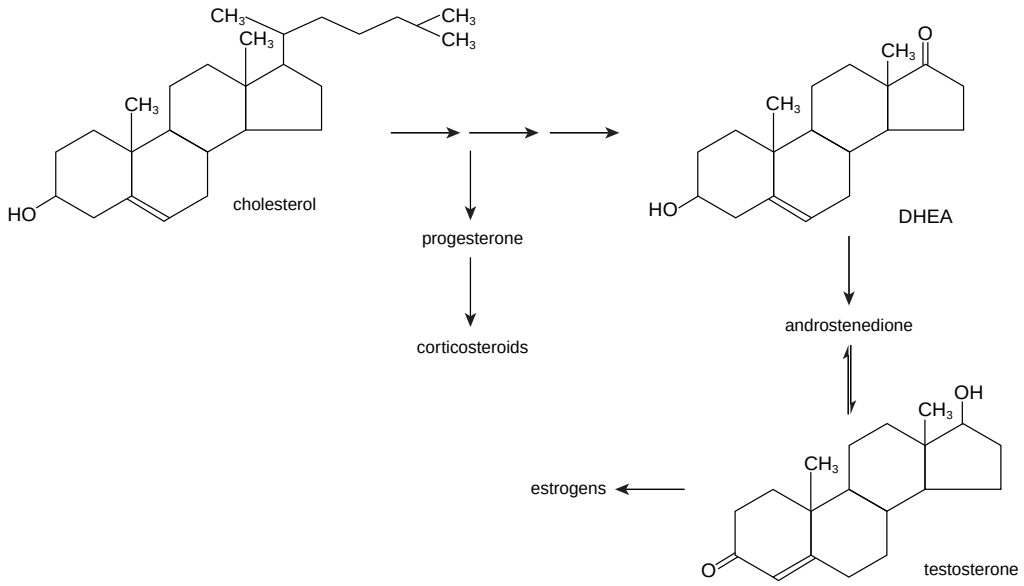
Figure 1

Relationship of androstenedione to other hormones



were unchanged in all subjects. LH, FSH, and estriol levels did not change. Estradiol levels were significantly ($P < 0.05$) higher at weeks 2 (+41%), 5 (+36%), and 8 (+27%) than at baseline. Estrone levels were significantly higher at weeks 2 (+44%) and 5 (+34%) than at baseline. Estrogen increases occurred in all subjects taking androstenedione and none taking placebo. Additionally, serum HDL cholesterol was 12% lower after two weeks of androstenedione, and remained lower to week 8 ($P < 0.05$).

Adverse Effects

Although no adverse effects were reported, the elevated hormone levels found in King's study raise concerns. Increased serum estrogen levels have been associated with gynecomastia and increased risk of breast cancer in women and pancreatic cancer in men.[12] Endogenously elevated androstenedione serum concentration has been observed to increase the risk of prostate cancer,[13] though not in every study.[14] Elevated androstenedione has been associated with increased risk of pancreatic cancer[15] and leads to hirsutism.[6] Lowered HDL cholesterol levels are independently associated with higher risk for cardiovascular disease. No studies are available on the adverse effects of long-term androstenedione use.[16] The diabetes detected during King's study was not reported as an adverse effect due to androstenedione.

Regulation

Androstenedione is banned by the National Football League, the National Collegiate Athletic Association, and the International Olympic Committee. The Association of Professional Team Physicians has recommended that it be banned from all competitive sports and taken off the market.[17] The American College of Sports Medicine has called for reform of DSHEA because it fails to regulate drugs like androstenedione.[18]

Drug Interactions

One review reported that AAS in general increase sensitivity to oral anticoagulants and antidiabetic medications, but gave no further details.[9] Reports of drug interactions with androstenedione itself were not found.

Formulation

Tablets and capsules contain 50 or 100 mg androstenedione. Manufacturers recommend 100-300 mg/d, though some go as high as 1,200 mg/d.[1] Androstenedione is also available as a nasal spray, sublingual spray, and percutaneous gel. The nasal spray patented in Germany delivers 3.5-15 mg androstenedione per pump.[8]

Conclusion

King's RCT provides clear evidence of adverse blood chemistry changes, and the scant data available provide no evidence that androstenedione has the effects athletes seek. The older data are poor in quality, but provide some support for a short-duration effect, possibly increasing aggressiveness. The single published RCT conflicts with prior claims that androstenedione boosts testosterone levels. However, the RCT used male nonathletes, and the effects may be different in trained

athletes and in females. Further research is needed before King's efficacy conclusions can be generalized to those more likely to use androstenedione.

Recommendation

Given the lack of demonstrated efficacy and the significant potential for adverse effects, discourage the use of androstenedione. ❖

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Chamomile for Use as Anti-inflammatory, Antispasmodic, and Sedative

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

INFLAMMATORY SKIN CONDITIONS AND SYSTEMIC processes are often seen and treated in clinical practice. Although usually not life threatening, conditions such as eczema, dermatitis, and oral mucositis can lead to significant morbidity and make life miserable.

Treatment of these medical conditions may involve the use of either topical or systemic steroids and nonsteroidal anti-inflammatory agents, all of which have significant side effects. Despite the lack of clinical trial data, chamomile has been used historically as an anti-inflammatory, antispasmodic, and calming agent.[1] In fact, chamomile sales exceeded $8.3 million in Germany alone in 1996, making it one of the most popular (and all-purpose) herbal therapies in the world.

History

Chamomile (*Matricaria recutita*), also known as German chamomile, belongs to the Asteraceae family and is an annual herbaceous plant indigenous to Europe and Western Asia.[2] Roman chamomile (*Chamaemelum nobile*) represents another popular plant type from the same family.[2] Although German chamomile accounts for a majority of sales and scientific study, both have been used as medicinal plants for centuries.[2]

The name chamomile comes from the Greek *chamos* meaning on the ground and Greek *melos* meaning apple—indicative of chamomile's aroma which resembles that of apples.[2] Flower heads of the plant are harvested in summer during the beginning of flowering when essential oil content is highest.[2]

The medicinal use of chamomile dates back to the Egyptians who "dedicated chamomile to their gods and to the sun, due to its power to cure agues [fever]."[3] Chamomile later was used by Sir William Culpeper who recommended it as an anti-inflammatory and digestive aid.[2] The German phrase for chamomile, *alles zutraut*, or "cure all," attests to the high regard for chamomile in that country.[4] Today, chamomile is most commonly used for wound healing, to treat inflammatory skin conditions, and as a food additive. It is also commonly used for minor digestive disorders and as a mild sedative.

Pharmacology

The therapeutic actions of chamomile derive from compounds contained in its essential oil, derived from its flower head.[1] Constituents of the essential oil possessing the principal anti-inflammatory and antispasmodic properties include the terpenoids (α-bisabolol oxide A, α-bisabolol oxide B, (–)-α-bisabolol, farnesene, and chamazulene [a breakdown product of matricine]).[5] Other active constituents of the plant include flavonoids, most notably apigenin and luteolin, along with coumarins (herniarin), amino acids, and tannins.

Mechanism of Action

Chamomile compounds exhibit numerous pharmacological properties. Anti-inflammatory effects have been demonstrated from both whole alcoholic extracts as well as individual constituents isolated from them. Most studies, however, have found that the whole extracts were more active than their individual constituents.[6] Constituents of chamomile act mainly on the inflammatory mediators of the arachidonic acid cascade, probably by inhibition of 5-lipooxygenase and cyclooxygenase.[6] In animal models, bisabolol effectively reduced inflammation and arthritis and has reduced healing time of cutaneous burns.[7]

Chamazulene exerts anti-inflammatory and anti-allergic activity. Several flavonoid components (including apigenin and luteolin) also exert anti-inflammatory properties and have been noted in vitro to have anti-inflammatory potencies similar to that of low-dose indomethacin.[1]

Finally, reported antispasmodic and sedative activity of chamomile extracts[8] may derive from the action of apigenin, which binds to central benzodiazepine receptors.[9]

Animal Studies

There are numerous animal studies evaluating the anti-inflammatory effects of chamomile extracts and specific components. In a study utilizing 1 ml of chamomile extract containing 50 mg of a standardized dry product, mice were exposed to topical croton oil applied to the ear to induce edema.[10] Controls were compared to mice given chamomile extract, 0.75 mg hydrocortisone, and benzydamine, a non-steroidal anti-inflammatory agent. Chamomile extract was found to reduce edema nearly as well as benzydamine but less than hydrocortisone. Another study of experimentally induced ear edema in mice utilized the flavonoid apigenin, which also was found to be effective.[11]

In addition, essential oil of chamomile was found to be comparable to papaverine in reducing experimentally induced spasm of isolated guinea pig small intestine resulting in decreased tonus and peristalsis.[12] These effects were found to be dose dependent. Specific components, including (–)-α-bisabolol and apigenin, were found to have the most significant effects. Additionally, (–)-α-bisabolol was noted to inhibit the occurrence of stomach ulceration following administration of indomethacin, stressful stimuli, or alcohol to rats.[13]

Clinical Trials

Chamomile extract has been evaluated in a number of clinical trials. Most have involved the use of chamomile topically to aid and prevent mucositis and dermatitis. In the largest and most recent double-blind, randomized, placebo-controlled study (DBRCT), 164 patients receiving 5-fluorouracil-based chemotherapy were given chamomile or placebo mouthwash tid for 14 days.[14] Results revealed no difference between chamomile and placebo.

In contrast, a previously published case series revealed positive results. Ninety-eight patients were treated with chamomile oral rinse during head and neck irradiation and/or systemic chemotherapy.[15] In this study, 20 patients treated with radiation and 46 patients receiving systemic chemotherapy were given prophylactic care using chamomile rinse. Thirty-two patients were treated after mucositis had already developed. With prophylactic use of chamomile, only one of the 20 patients receiving radiation therapy developed grade 3 mucositis in the final week of treatment and only 10 of the 46 patients receiving chemotherapy developed clinically significant mucositis. Of the 32 patients receiving chamomile therapy for existing mucositis, all noted immediate relief from discomfort and showed improvement.

In another DBRCT assessing effect on inflammation, 48 women who underwent surgery for local breast cancer

were randomized to receive almond ointment or chamomile cream to the affected breast while undergoing radiation therapy.[16] No statistically significant differences were noted between the two groups. Neither agent could prevent radiation-induced skin changes. Patients however preferred the chamomile cream because it was absorbed rapidly and did not stain.

Finally, a multicenter clinical trial found German chamomile to be 60% as active as low dose (0.25%) hydrocortisone when applied topically for atopic dermatitis.[17]

Chamomile's effect as an antispasmodic has been evaluated in a DBRCT of 68 healthy, term infants (ages 2-8 weeks) with colic, which was defined as spells of unexplained irritability, agitation, fussiness, or crying, which lasted more than three hours a day, three times a week for at least three weeks. Infants were randomly assigned to receive an herbal tea containing German chamomile, vervain, licorice, fennel, and balm-mint, or placebo (hot water/glucose infusion). With every colic episode, each infant was offered 150 ml of herbal tea or placebo; each infant received no more than three doses per day. After seven days of therapy, colic symptom scores were 57% improved in the herbal tea group compared to 26% improvement with placebo ($P < 0.01$).[18]

Other human studies showing modest benefits from the use of chamomile for a variety of indications have been of poor methodological design and have lacked proper statistical power. One example is the often quoted study in which 12 hospitalized patients consumed two cups of chamomile tea while undergoing cardiac catheterization.[19] The average cardiac index decreased minimally from 3.00 to 2.88 l/min/m^2. Stroke index remained unchanged and a slight increase in the mean brachial artery pressure from 91 to 98 mm Hg was observed ($P < 0.05$). Interestingly, 10 minutes after the ingestion of the tea, 10 of 12 patients fell asleep. To date, no randomized trials investigating chamomile's purported sedative effects have been published.

Adverse Effects and Interactions

Chamomile is generally regarded as safe (GRAS) by the FDA as a spice, seasoning, or flavoring agent. It is listed as a Class 1 herb by the American Herbal Products Association's Botanical Safety Handbook, noting that it can be safely consumed when used appropriately. In animal studies, both the oral LD_{50} (dose lethal to 50% of the animals) and the dermal LD_{50} exceeded 5 g/Kg of body weight.[8] An LD_{50} value in mice given oral chamomile has been documented to be 2.5 ml/Kg. Long-term oral administration of chamomile extracts to rats produced no teratogenicity or signs of changes in prenatal development. No drug-herb interactions have been associated with chamomile to date.[6]

Several cases of significant allergic reactions to chamomile have, however, been reported. One 35-year-old with a known history of ragweed/hay fever ingested one cup of chamomile tea and developed angioedema and subsequent anaphylaxis.[20] In another case, a 54-year-old also developed an anaphylactic reaction after

Table 1

Examples of available commercial chamomile products

Product	Formulation	Manufacturer's Recommended Dose	Price/Count
Dermatologic Product			
Abkit CamoCare® Gold Chamomile Face Lift	Camillosan™ chamomile extract, alpha+beta hydroxy cream	Smooth cream on face 1-2 times/d	$7.63/2 oz
Oral Preparations			
Nutritional Dynamics German chamomile	400 mg chamomile flower per capsule (standardized to 1% apigenin, 0.5% essential oil)	1-2 capsules/d	$12.95/60 capsules
Nature's Way German chamomile	125 mg extract (standardized to 1.2% apigenin)	1-2 capsules as needed for anxiety, insomnia	$11.49/60 capsules
Herbal Plus German chamomile	250 mg (non-standardized) per capsule 4:1 extract	1-2 capsules/tid	$9.99/30 capsules
Nature's Way	350 mg chamomile flowers per capsule (0.5% essential oil potency guaranteed)	2 capsules/bid	$7.99/100 capsules
Nature's Herbs chamomile flowers	354 mg chamomile flowers per capsule	2-3 capsules/d	$7.99/100 capsules
Harvest of Nature chamomile tea	2 oz/bag whole herb	1-2 cups/d	$4.69/24 bags

Source: Online mail-order firms and retail stores

ingestion of chamomile tea.[21] Both patients had a history of ragweed allergies; both responded quickly to standard treatment. Rare reports of contact dermatitis after topical application have been noted.[8] Patients with known allergies to plants such as ragweed, asters, and chrysanthemums should avoid contact with chamomile products.[8] In addition, whole chamomile may be contaminated with other related, more allergenic plants.

Chamomile has other effects. Excessive use of chamomile may result in mild gastroparesis and emesis.[8] Chamomile should not be used in the eyes because of residual alcohol content. Although low doses of (–)-α-bisabolol have been administered orally to pregnant rats with no reported effects on the fetus, use of chamomile by pregnant and lactating mothers should be avoided.[6] Chamomile has been reputed to affect the menstrual cycle. Teratogenicity studies in vitro have been documented for (–)-α-bisabolol with oral toxicity at high doses; a dose of 3 ml/Kg has been found to increase the number of fetuses reabsorbed and to reduce body weight at birth.[5]

Formulations and Dosing

Although available products may contain either German chamomile or Roman chamomile, the majority of studies performed both in animals and humans involved the product Kamillosan®.[6] Manufactured by Chemiewerke Homburg Pharmaceuticals in Frankfurt, this product has been marketed since 1921 and utilizes a German chamomile extract.[6]

In addition to teas, tinctures, liquid extracts, salves, creams, and capsules, chamomile is often added to soaps and perfumes, given its pleasant smell.[8] Historical use as a compress, rinse, and gargle continues today. Because it is approved as a food additive by the FDA, chamomile is also commonly added to herbal beverages. Several commercial preparations are available in the United States. (*See Table 1.*)

According to the German Commission E, dosing of chamomile as a tea means pouring 150 cc of boiling water over 3 g dry weight of fresh or dried flower heads and steeping for 5-10 minutes.[1] Foster recommends steeping a gallon of flowers in 30 gallons of hot water for a soothing, antihemorrhoidal bath. Many chamomile preparations are standardized to contain a minimum value of chamazulene and α-bisabolol; in the German pharmacopeia, the crude drug must contain at least 0.4% volatile oil. Unfortunately, there is no universally accepted standardization of chamomile products.

Conclusion

Although published, randomized controlled trials have revealed conflicting results regarding efficacy, chamomile appears to have potential for adding to currently available treatments for a number of commonly encountered conditions, including inflammatory skin conditions. Certainly DBRCTs are needed to establish efficacy. As an FDA approved food additive and as a substance generally regarded as safe, chamomile's risk of significant toxicity appears very low, with several notable exceptions.

Recommendation

Given its long history of use, apparent safety, and documented bioactivity in animal studies, consideration might be given to using chamomile extract for mild skin irritation and inflammation, mild anxiety/insomnia, and intestinal colic symptoms. Chamomile creams might also be considered for mild skin irritation. Pregnant and lactating women and patients with known allergies to ragweed and other members of the Asteraceae family should avoid chamomile. ❖

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Aerobic Exercise for Fatigue in Multiple Sclerosis

By V. Jane Kattapong, MD, MPH, MA

MULTIPLE SCLEROSIS (MS), A FRIGHTENING CHRONIC degenerative disease first described by the French neurologist Charcot, largely affects young adults. Typically, the onset occurs between ages 30 and 50.[1] Fatigue is one of the most common symptoms of MS. One MS specialist reports that his patients "often say they could manage the problems and symptoms that MS brings if they just were not so fatigued and had more energy."[2] The triple, energy-draining whammy of career, family, and MS can be devastating. Therefore, MS patients may benefit greatly from fatigue-relieving therapy.

Course and Therapy

MS is characterized by recurrent attacks or chronic progression of disability. Disability results not only from neurological deficits, but also from other symptoms associated with MS, including fatigue, depression, and a decrease in self-rated quality of life. As a result, the ability to perform daily activities is even more impaired than neurologic deficits would predict.[3]

Since there is such disability and no pharmacological "cure" for MS, many patients seek alternative therapies. One survey of MS patients determined that physical therapy is the most common non-pharmacological, "alternative" therapy obtained.[4] Similarly, primary care practitioners feel acceptance toward exercise counseling as a "legitimate" medical therapy.[5] Despite this acceptance, the prevalence of physician-based exercise counseling, in general, is low,[6] and it is likely that the prevalence of physician-based exercise counseling for MS patients is even lower than that of the general population.

Pathophysiology

In MS, multifocal inflammation results in areas of demyelination in the central nervous system (CNS). The demyelinated areas, called "plaques," lead to slowed impulse conduction in the CNS. Typically, the pyramidal, cerebellar, or optic tracts are involved.[7] Weakness, sensory loss, balance disturbances, visual loss, and other deficits commonly occur.

Although the pathogenesis of MS is poorly understood, several well-designed studies have implicated a role for autoimmune dysfunction.[8] Immunomodulation is one promising avenue for treatment.[9] Moderate exercise appears to enhance immune function, and high intensity or prolonged exercise appears to depress immune function. However, the immunomodulatory effect of exercise is not well understood.[10]

Pathophysiology of Exercise in MS

Exercise provides an outlet for social interaction and relaxation. Exercise may also increase core body temperature, however, and this is problematic for MS patients. In MS, an elevation of core body temperature as slight as 0.5° C can result in a transient increase in focal neurological symptoms, such as weakness or blurred vision. Known as Uhthoff's phenomenon,[11] this symptom change may occur because demyelinated nerve fiber conduction is extremely sensitive to temperature elevation, which slows nerve conduction. Deficits therefore become more prominent. Because exercise

may increase core body temperature, which may lead to transient worsening of symptoms, physicians treating MS patients traditionally recommended limiting or avoiding aerobic exercise. However, this recommendation is not evidence-based.

Clinical Trials

Little information exists regarding benefits of regular aerobic exercise for MS patients. A literature search revealed only one randomized trial. In this study conducted at the University of Utah, a 15-week aerobic training program involved MS patients recruited through the MS Society and through physician referrals in Salt Lake City, Utah. Fifty-four patients were randomly assigned to exercise or non-exercise groups.[12] Neurological evaluation, physiological measurements, and psychological instruments were completed at baseline and after study completion.

All patients had mild-to-moderate disability, with Kurtzke Expanded Disability Status Scale (EDSS) scores of 6.0 or less.[13] Measurements included validated, pretested instruments known as the profile of mood states (POMS), the sickness impact profile (SIP), and the fatigue severity scale (FSS). A combined arm and leg ergometer, computerized force measurements of maximum voluntary isometric contractions, and body composition analyses were also obtained.[14]

Three supervised training sessions per week were administered to the exercise group for 15 weeks. At each session, patients participated in a five-minute warm-up period at 30% of maximum aerobic capacity (VO_{2max}), 30 minutes of activity at 60% of VO_{2max}, and a five-minute cool-down, plus five to 10 minutes of stretching during the session. Cooling was achieved via air fans and ergometer airflow.

Eight patients dropped out during the course of the study—six for reasons unrelated either to their MS or the study and two because of MS exacerbations. MS exacerbations that occurred in participants were distributed equally between the exercise and non-exercise groups.

VO_{2max} increased significantly (by 22% vs. 1% in the non-exercise group) after 15 weeks. Significant increases over baseline in upper and lower extremity strength, and significant decreases in skinfolds, triglyceride levels, and very-low-density lipoprotein levels were found in the exercise group. Other significant physiological measures are outlined in Table 1. Patients in the exercise group experienced significant decreases in depression, anger, and fatigue at 10 weeks according to the POMS. On the SIP, patients in the exercise group reported significant improvements in ambulation, mobility, and in body-care and movement scores at 10 weeks.[12] These improvements in psychological indicators continued, but were no longer statistically significant at 15 weeks. No adverse effects resulting from the intervention were reported.

Table 1
Selected physiological measures, MS exercise group

	Baseline	15 weeks
VO_{2max} (ml/Kg/min)	24.2	29.4
Physical work capacity (W x min)	913	1351
Shoulder flexion (newtons)	165	183
Knee extension (newtons)	255	289

Adapted from: Petajan JH, et al. Impact of aerobic training on fitness and quality of life in multiple sclerosis. *Ann Neurol* 1996;39:432-441.

Although this study evaluated the effects of aerobic exercise, which improves cardiorespiratory endurance, Tai Chi Chuan and martial art therapy have been reported to confer health benefits as well.[15,16] However, the effects of Tai Chi Chuan and martial art therapy in MS have not specifically been studied.

Conclusion

According to the results of a single randomized study, aerobic exercise in mild-to-moderate MS appears to confer the same fitness and psychological benefits that it does in patients without MS. Although the study was not designed to improve muscle strength, favorable changes in isometric force were found as well. Additionally, more long-term study of the effects of exercise on MS patients will be necessary to explore whether exercise might favorably alter the rate of disease progression.

Recommendation

With proper attention to avoidance of overheating, maintaining a regular aerobic exercise program may help MS patients limit disability caused by fatigue and depression. Although the patients in this program participated in a specialized, medically supervised program, MS patients who have received permission from their physicians should be able to reap similar benefits from aerobic exercise programs primarily intended for the general public. Such general exercise programs may need to take into account the special requirements of MS patients and allow them to "tone down" the difficulty of the regimen. MS patients should never be expected to "push their limits" beyond the personal comfort zone, and most certainly should not exercise to the point of exhaustion. Pre-exercise cooling and employment of cooling devices such as air fans during the exercise

period are advisable.[12] Exercise in cool water may be an ideal form of exercise for MS patients. However, depending on each individual's specific physical deficits, almost any form of exercise could be adapted appropriately. This study offers welcome encouragement to MS patients to continue to "stay fit," despite their chronic disability. ❖

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CME Questions

12. Which of the following categories best describes the effects of androstenedione?
a. Anabolic
b. Androgenic
c. Both anabolic and androgenic
d. Neither anabolic nor androgenic

13. Athletes using androstenedione and other AAS should be closely monitored if they are also taking medication for:
a. depression.
b. bacterial infections.
c. anti-inflammatory effects.
d. diabetes.

14. All studies to date have shown chamomile to possess benefit in the treatment of chemotherapy-induced mucositis.
a. True
b. False

15. Infants with colic were shown to benefit from:
a. tea containing German chamomile alone.
b. tea containing Roman chamomile alone.
c. tea containing a combination of herbs.
d. No benefit from herbs was noted.

16. A recent randomized trial studying the effect of aerobics on MS patients found:
a. significant increases in upper and lower extremity strength.
b. significant increases in skinfolds, triglyceride levels, and very-low-density lipoprotein levels.
c. significant increases in depression, anger, and fatigue.
d. All of the above.
e. None of the above.

With Comments from John La Puma, MD, FACP

Oral L-Arginine for Interstitial Cystitis

Source: Korting GE, et al. A randomized double-blind trial of oral L-arginine for treatment of interstitial cystitis. *J Urol* 1999;161:558-565.

NITRIC OXIDE SYNTHASE ACTIVITY IS decreased in the urine of patients with interstitial cystitis. In a preliminary trial, oral L-arginine, the substrate for nitric oxide synthase, increased urinary nitric oxide synthase activity and improved interstitial cystitis symptoms.

A total of 53 interstitial cystitis patients were randomly assigned to receive daily 1,500 mg L-arginine or placebo orally for three months. Interstitial cystitis symptoms were assessed by interviews at two weeks, and one, two, and three months. The trial was completed by 21 of 27 patients in the L-arginine group and 25 of 26 in the placebo group. Using per protocol analysis, 6/21 (29%) patients in the L-arginine group and 2/25 (8%) in the placebo group were clinically improved by the end of the trial (P = 0.07). A Likert scale showed greater global improvement in the L-arginine group (10/21, 48%) than in the placebo group (6/25, 24%) at three months (P = 0.05) with a decrease in pain intensity (P= 0.04), and tendency toward improvement in urgency (P = 0.05) and frequency of pain (P = 0.09). Using an intention to treat approach, there were no differences between the groups.

We conclude that oral L-arginine may decrease pain and urgency in a subset of interstitial cystitis patients.

COMMENT

A successful pilot study with more hands-on attention than their intervention helped these Yale investigators to gain NIH support for this double-blind investigation. Only after three months was there a demonstrable difference between L-arginine and placebo patients. Patients with greater than a 800 cc bladder capacity and a history of recurrent genitourinary infections were the two subgroups that experienced improvement. Adverse effects were not described, although four of the six or seven (per the authors) who withdrew from the arginine group complained of increased pain, not decreased pain.

Oral L-arginine is also touted for nonobstructive coronary disease. (See *Alternative Medicine Alert*, June 1999, p. 72.) It seems to have beneficial effects, but also "has been reported to activate herpes virus replication and interact, in animal models, with tumor growth."

Recommendation

In patients with interstitial cystitis refractory to standard measures, who are willing to risk actually increased pain, who are not immunosuppressed, and who do not have a history of herpes activation, oral L-arginine may be worth a try. If it does work, it will probably take three months. Be cautious. ❖

Lycopene for Prostate Cancer

Source: Gann PH, et al. Lower prostate cancer risk in men with elevated plasma lycopene levels: Results of a prospective analysis. *Cancer Res* 1999;59:1225-1230.

DIETARY CONSUMPTION OF THE CAROTenoid lycopene (mostly from tomato products) has been associated with a lower risk of prostate cancer. We conducted a nested case-control study using plasma samples obtained in 1982 from healthy men enrolled in the Physicians' Health Study, a randomized, placebo-controlled trial of aspirin and beta-carotene. Subjects included 578 men who developed prostate cancer within 13 years of follow-up and 1,294 age and smoking status-matched controls.

We quantified the five major plasma carotenoid peaks (alpha- and beta-carotene, beta-cryptoxanthin, lutein, and lycopene) plus alpha- and gamma-tocopherol and retinol using high-performance liquid chromatography.

Lycopene was the only antioxidant found at significantly lower mean levels in cases than in matched controls (P = 0.04 for all cases). The odds ratios (OR) for all prostate cancers declined slightly with increasing quintile of plasma lycopene; there was a stronger inverse association of aggressive prostate cancers (5th quintile, OR = 0.56, confidence interval [CI] = 0.34- 0.91). In the placebo group, plasma lycopene was very strongly related to lower prostate cancer risk (5th quintile OR = 0.40; P trend = 0.006 for aggressive cancer), whereas there was no evidence for a trend among those assigned to beta-carotene supplements. However, in the beta-carotene group, prostate cancer risk was reduced in each lycopene quintile relative to men with low lycopene and placebo. The only other notable association was a reduced risk of aggressive cancer with higher alpha-tocopherol levels that was not statistically significant. None of the associations for lycopene were confounded by age, smoking, body mass index, exercise, alcohol, multivitamin use, or plasma total cholesterol level.

A recent prospective dietary analysis noted that for men with low lycopene levels, beta-carotene supplements were associated with risk reductions comparable to those observed with high lycopene levels. Increased consumption of tomato products and other lycopene-containing foods might reduce the occurrence or progression of prostate cancer.

COMMENT

The print ads showing lycopene pouring from a squeezable bottle are finally giving middle-aged male Cubs fans something to cheer about. The

theory is this—if lipid soluble antioxidants like lycopene and other carotenoids can protect DNA and membrane lipids from oxidation, then fewer neoplasms will result. Lycopene is stored in the prostate and cannot be converted to vitamin A, making it relatively more available in the tissue.

The results from this study of 22,000 physicians hinge on a single baseline plasma sample to characterize long-term levels of circulating lycopene. Higher lycopene levels are associated with lower risk of developing prostate cancer in those men not taking beta-carotene supplements. Men taking beta-carotene did not have a significantly lower risk of developing prostate cancer when compared with men taking placebo. Those men taking beta-carotene who also had high lycopene levels did not get additional protection from them.

Cooked tomato products have more lycopene than fresh or dried tomatoes. Because lycopene is fat-soluble, oil improves its bioavailability. It seems that gently warmed heirloom tomato slices sprinkled with roasted garlic, ribbons of arugula, toasted pine nuts, and extra virgin olive oil really can be good for the old prostate. A recent comprehensive review in the *Journal of the National Cancer Institute (*1999;91: 317-331) emphasized that purified lycopene supplements have not been tested—only red tomatoes (and pink grapefruit, apricots, and watermelon).

How much is enough to reduce prostate cancer incidence? No one knows—or even if it's the lycopene that is conferring the benefit. But this food can't harm, and from these data, it may well help.

Recommendation

Men at risk for prostate cancer cannot hurt themselves by eating more simmered marinara, roasted tomato sauce, or sauteed tomato salsa. Tell men to have some every day—for the flavor. ❖

Supplements for Institutionalized Elderly Patients

Source: Girodon F, et al. Impact of trace elements and vitamin supplementation on immunity and infections in institutionalized elderly patients: A randomized controlled trial. *Arch Intern Med* 1999;159:748-754.

ANTIOXIDANT SUPPLEMENTATION IS thought to improve immunity and thereby reduce infectious morbidity. However, few large trials in elderly people have been conducted that include end points for clinical variables. We sought to determine the effects of long-term daily supplementation with trace elements (zinc sulfate and selenium sulfide) or vitamins (beta-carotene, ascorbic acid, and vitamin E) on immunity and the incidence of infections in institutionalized elderly people. We conducted a randomized, double-blind, placebo-controlled intervention study including 725 patients over age 65 (mean age 83.9), institutionalized in 25 geriatric centres in France. Patients received an oral daily supplement of nutritional doses of trace elements or vitamins or a placebo within a 2 x 2 factorial design for two years.

Correction of specific nutrient deficiencies was observed after six months of supplementation and was maintained for their first year, during which there was no effect of any treatment on delayed-type hypersensitivity skin response. Antibody titers after influenza vaccine were higher in groups that received trace elements alone or with vitamins. The vitamin group had significantly lower antibody titers ($P < 0.05$). The number of patients without respiratory tract infections during the study was higher in groups that received trace elements ($P = 0.06$). Supplementation with neither trace elements nor vitamins significantly reduced the incidence of urogenital infections. Survival analysis for the two years did not show any differences between the four groups.

Low-dose supplementation of zinc and selenium provides significant improvement in elderly patients by increasing the humoral response after vaccination and could have considerable public health importance by reducing morbidity from respiratory tract infections.

COMMENT

These French investigators assessed the prevalence of nutrient deficiency by assessing serum value, and finding approximately 80% of patients to be deficient in selenium. Deficiencies were not significantly different across the groups. Supplemental zinc (20 mg) and selenium (100 mcg) were provided. Except for zinc, serum concentrations of vitamins reached a plateau after six months; zinc levels rose throughout the study, as zinc is absorbed slowly in older people. Adherence was very good—over 85%.

Trace mineral supplementation was associated with fewer respiratory tract infections—markedly so.

Measuring mineral levels is not yet a standard assessment, and for this indication, seems unnecessary. The cost of the needed intervention is small, the side effect profile favorable, and the therapy efficacious. Compared with colds in nursing homes, zinc and selenium supplements look great.

Recommendation

All residents of long-term care institutions over age 65 should take a trace mineral supplement of zinc and selenium, in addition to regular vitamins—about twice the U.S. RDI for vitamin C, beta-carotene, and vitamin E. ❖

In Future Issues:

Cranberry for Urinary Tract Infections

DHEA Supplementation During Menopause

Acupuncture for Depression