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Chromium Supplementation for Weight Loss

By Dónal P. O'Mathúna, PhD

SALES OF CHROMIUM SUPPLEMENTS GENERATE MORE THAN $100 MILlion annually.[1] Chromium picolinate is promoted as a "fat burner" and "muscle builder" for losing weight and enhancing athletic performance. The supplement also allegedly increases energy, curbs addictions, cures acne, prevents insomnia, relieves depression, and increases life span.

Physicians have not yet warmed to prescription pharmacological approaches to dieting, after the 1997 withdrawals of fenfluramine and dexfenfluramine, both associated with valvular regurgitation and primary pulmonary hypertension. The November 2000 Food and Drug Administration (FDA) recommendation to withdraw phenylpropanolamine, present in popular over-the-counter weight-loss medications and associated with stroke, is a more recent reminder of the danger of these medications.[2] Clinicians likely will receive more inquiries about the effectiveness and safety of chromium as a viable weight-loss alternative to the pharmaceuticals that remain, such as phentermine and sibutramine (Meridia®).

Biochemistry

Chromium is an essential trace element and part of the insulin metabolic pathway.[3] The USDA estimated safe and adequate daily dietary intake of chromium is 50-200 mcg for adults.[3] The Institute of Medicine (IOM) 2001 report on Dietary Reference Intakes concluded there was insufficient evidence to set an Estimated Average Requirement or a Tolerable Upper Intake Level (UL) for chromium.[4] In their place are Adequate Intake (AI) levels, which are the amounts expected to meet or exceed the daily requirements in essentially all healthy people. The AI level for chromium is 35 mcg/d for young men and 25 mcg/d for young women. A small number of studies have found little detriment from people consuming 15 or 5 mcg/d.[4] Clinical research is hampered by the analytical challenges of accurately measuring chromium levels, since only 0.5-2% of chromium in dietary sources is absorbed, and urinary levels occur in parts per billion.[4] There is no simple, reliable test for chromium deficiency.

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INSIDE

Pharmacology

Chromium deficiency was first reported in 1977 when patients on long-term total parenteral nutrition developed classic diabetic symptoms that were reversed with the addition of chromium to their diets.[5] Research on the potentially beneficial role of chromium in treating type 2 diabetes in chromium-deficient patients was reviewed here previously.[6] Because many overweight patients with type 2 diabetes can control their diabetes with effective weight management, and because chromium's mechanism of action involves glucose and insulin metabolism, there is interest in chromium as a weight loss agent.

Mechanism of Action

Normally, receptors on the surfaces of insulin-sensitive cells bind insulin. This allows these cells to absorb chromium which then binds a small protein (chromodulin) inside the cell.[1] The resulting complex then activates an enzyme called insulin receptor tyrosine kinase. This enzyme enhances glucose absorption and promotes fatty acid metabolism.

In contrast, "chromium deficiency" leaves cells desensitized to insulin (or "insulin resistant").[7] Less glucose enters cells for energy production and instead is stored as fat. Insulin resistance also hinders the passage of amino acids into muscle cells, reducing protein synthesis.[8] Chromium supplementation allegedly reverses these effects, leading to the "burning" of excess fat, weight loss, and increased muscle mass.

Clinical Studies

Clinical studies prior to 1998 were reviewed here previously;[9] it should be noted that chromium doses are reported in mcg, where 1 mcg = 0.001 mg. The 1998 review found one 1969 study reporting increased fat-free body mass and decreased body fat after chromium supplementation, and five studies reporting no significant benefits. For this update, six more studies of chromium for weight loss were found: two with positive results, three with negative results, and one with mixed results. Additionally, four other studies focused primarily on diabetic outcomes and found no changes in body composition. These are reviewed elsewhere.[6]

Two randomized, double-blind trials found positive effects from chromium supplementation, yet both had methodologic flaws that call their results into question. In the first, 154 adults were divided into three groups and received 0 mcg, 200 mcg, or 400 mcg chromium picolinate daily.[10] Subjects were instructed to consume "at least two servings" of a protein drink containing their assigned chromium dose. After 72 days, underwater displacement testing showed significantly reduced body fat in the chromium groups compared to placebo, but no significant difference between the two chromium groups. Amount of drink consumed, overall diet, and exercise frequency were not controlled.

In the second study, the same researchers randomly assigned 130 new subjects to groups taking capsules containing either 400 mcg chromium picolinate or placebo.[8] After 90 days, body composition was measured using dual energy X-ray absorptiometry. Changes in actual weight, percent body fat, and fat-free mass did not differ between the two groups, but the chromium group showed significantly reduced fat mass ($P = 0.023$). After statistical adjustments to control for dietary and exercise differences, significant differences were calculated for actual weight ($P < 0.001$), percent body fat ($P < 0.001$), and fat mass ($P < 0.001$). However, the significant differences were found only in calculated estimates of weight and fat loss based on energy expenditure, not the measured values.

A recent randomized, double-blind study involved 18 older men (56-69 years) assigned to take either placebo or 924 mcg/d chromium picolinate in two capsules.[11] Twice weekly all men participated in a supervised, resistance-training workout. Diet and urinary chromium levels were monitored. Although body composition and

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muscle strength changed during the study, no significant differences existed between the two groups.

Another randomized, double-blind study involved 19 healthy men and women aged 63-77 years.[12] Subjects received either a placebo or 1,000 mcg/d chromium picolinate (divided equally between morning and evening). After eight weeks, no significant differences were found between the groups in body composition, insulin sensitivity, or serum lipids.

The third study with negative results examined 29 moderately obese patients at risk for developing type 2 diabetes.[13] Subjects were given nutrition counseling in an effort to maintain their body weight and randomly assigned to either 1,000 mcg/d chromium picolinate or placebo for eight months. Significant improvements in insulin responses occurred in the chromium subjects, but no significant changes occurred in body weight, abdominal fat distribution, or body mass index.

One study examined the effect of both exercise and chromium supplementation in 43 mildly obese women.[14] Those who took 400 mcg/d chromium picolinate for nine weeks but did not exercise had significant gains in body weight, fat-free mass, and fat mass. However, those who took 400 mcg/d chromium nicotinate and exercised aerobically had a small but statistically significant loss in body weight, and no significant change in fat-free mass or fat mass.

Adverse Effects

Chromium supplements are believed to be safe, with no clinical studies reporting adverse reactions. The IOM report found insufficient evidence to set a UL.[4] Rats given several thousand times the equivalent of 200 mcg/d chromium in humans showed no adverse effects.[15] However, four case reports of adverse effects exist, describing renal failure, liver dysfunction, short-lasting psychological changes, and acute generalized exanthematous pustulosis.[6] The FDA has received more than 500 adverse event reports involving chromium supplements, though most involve dietary supplements containing numerous herbs and other agents.[16]

In vitro studies have demonstrated that chromium picolinate can produce chromosomal damage in hamster ovary cells[17] and can cleave DNA in solution.[18] Although the former study used doses vastly in excess of normal physiological levels, the latter occurred within physiological ranges. Chromium picolinate's unique stability gives it good absorption, but also allows accumulation in body tissues, leading to concerns about long-term side effects.

Drug Interactions

No adverse drug interactions have been reported. However, ascorbic acid, aspirin, and indomethacin markedly increase chromium absorption, while antacids lower absorption.[3] Diets high in complex carbohydrates, not simple sugars, increase chromium absorption.[3] Potential interactions may occur with drugs affecting glucose or cholesterol levels, or with corticosteroids.[19]

Formulation

Trivalent Cr^{3+} is the form found almost exclusively in foods, especially brewer's yeast, liver, American cheese, cereals, and wheat germ. However, chromium content in foods is highly variable, and processing can either increase or decrease the level.[4] The search for the biologically active form of chromium led to the extraction of glucose tolerance factor (GTF) from yeast.[20] This complex contains chromium, nicotinate, and three amino acids. Various GTF formulations are marketed as the safer, more natural form of chromium.

However, GTF's structure remains uncertain, and early conclusions about its role in glucose metabolism have been shown to be in error. While GTF makes chromium available to chromium-deficient animals, it inhibits insulin in animals with normal chromium levels.[1] GTF is now regarded as an artifact of its harsh extraction conditions and its value as a dietary supplement is questionable.[1]

The identification of nicotinate in GTF led to interest in its closely related isomer, picolinate. Chromium(III) picolinate is now the most commonly used form, usually prepared in 200 mcg capsules. Many products contain smaller amounts of chromium picolinate along with numerous herbs and minerals.

Conclusion

Chromium's essential role in insulin metabolism is well-established. Supplementation in chromium-deficient diabetics may offer some benefits, but not for those consuming adequate dietary chromium.[6] However, most trials using chromium picolinate supplements, with or without exercise, found no significant benefit for weight loss or percent body fat reduction. The three trials finding some benefit had serious methodological weaknesses. Research is lacking on the long-term effects of consuming chromium picolinate.

Recommendation

Chromium supplementation offers little, if any, benefit to patients attempting to lose weight. While some controversy exists over the possibility of serious harmful effects, these have not been observed in clinical trials. Diabetic patients should not take chromium without first consulting their physicians and monitoring their blood

glucose closely. For those attempting to lose weight, reducing caloric intake, increasing exercise, modifying eating behaviors, and enlisting others' support remain the foundations for success. ❖

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Light Therapy for Seasonal Affective Disorder (SAD)

By Barak Gaster, MD

"IN THE DARK OF WINTER LET THERE BE LIGHT." SO reads the menu of a trendy café in Helsinki, where Danish pastry and coffee may run $7, but the use of the light box at the table is free.

Seasonal affective disorder (SAD), the official name for depression occurring at the onset of winter and resolving with spring, affects an estimated 10 million Americans.[1] Thousands of people who suffer from SAD consider artificial light therapy to be therapeutic, and dozens of companies market light-therapy devices.

The first therapeutic light box was built in the early 1980s by researchers at the National Institutes of Mental Health, who reported the dramatic remission of seasonal depression in a 63-year-old engineer. In the 20 years since, a large amount of data have accumulated supporting the safety and efficacy of light therapy for the treatment of SAD.

Mechanism of Action

The precise pathophysiology of SAD is unknown.

Table 1

Light therapy devices

Device	Brightness	UV light source	Price
SunRay I	10,000 lux at 18.5"	non-UV	$319
WinterBright™	10,000 lux	UV shielded	$299
SunnyDays™ Desk Lamp	10,000 lux at 10"	non-UV	$219
NorthStar 10,000	10,000 lux at 26"	non-UV	$199
Sadelite	10,000 lux	non-UV	$189

Source: On-line mail-order firms

Since 1980, it has been known that exposing the retina to bright light suppresses melatonin production by the pineal gland. In 1982, when light therapy was shown to be effective for the treatment of SAD, the obvious explanation was that it caused phase shifting of the circadian rhythm of melatonin production in the brain.

Since then, further research has shown that light's effects on melatonin can only partly explain the efficacy of light therapy.[2] Other possible mechanisms of action include bright light's effects on 1) serotonin activity, 2) retinal sensitivity, or 3) cortisol regulation.[3] Studies suggest that retinal stimulation is required for light therapy to work.

Clinical Studies

There have been more than 60 randomized, controlled trials of light therapy for SAD. Almost all have shown a positive effect.

The placebo effect is a serious problem in light therapy research, because light therapy is almost impossible to test in a truly blinded fashion. In addition, almost all the patients who have participated in studies of light therapy have been recruited with media advertisements, such that almost all of those who enroll in trials begin with a strong belief that light therapy works. The two best studies have attempted to address this difficult research problem.[4,5]

In the first of these studies, Eastman randomized 96 patients to either morning light, evening light, or placebo.[5] Patients in the treatment groups received bright light (6,000 lux) for 1.5 hours/d, while the placebo group was exposed to a sham device. Patients in this placebo group were told that the sham device would expose them to a high concentration of negative ions, approximating the high concentration of negative ions in summer air. To increase patients' belief that sitting in front of the device would be beneficial, the device made a humming noise. Patient questionnaires at entry into the study and just prior to treatment suggested that most patients were convinced that negative ion therapy and bright light had an equal chance of working.

The proportion of patients who had more than a 50% reduction in their depression scores at the end of four weeks was significantly greater in the treatment groups than in the placebo group (61% morning light, 50% evening light, 32% placebo, $P < 0.05$ for the comparison between treatment groups and placebo).

In the second of these studies, Terman randomized 158 patients to bright light, a high-intensity negative ion generator, or a low-intensity negative ion generator.[4] The ion generators in this study in fact did generate negative ions. Patients exposed to light therapy had a 30% higher response rate than those receiving low-intensity negative ions, while the high-intensity ion group had an intermediate response.

Finally, additional research has been summarized in two meta-analyses. One reported on the results of 14 trials (total of 322 patients) which found that patients who received an average of 2,500 lux daily had significant improvement in their depression scores compared to patients who were exposed to dim light only.[6] Another more recent meta-analysis found a dose-response relationship between the intensity of light therapy and its antidepressant effect.[7]

Adverse Effects

Light therapy is generally well tolerated. About 15% of patients experience mild eye strain or headache, which can be eliminated by having patients sit either further from the light or for a shorter time each day.[8] It is not known whether this reduces effectiveness. Similar rates were reported for light intensities up to 10,000 lux.[9]

There are no known contraindications to light therapy, and no evidence that light therapy is associated with ocular damage.[8,10] Patients with eye disease or those who are at high risk for eye disease, such as those with macular degeneration, glaucoma, cataracts, or diabetes, should consult with an ophthalmologist prior to starting light therapy.[8] No harmful light/drug interactions have been reported.[11]

Light Intensity and Duration

Most studies of light therapy in the 1990s exposed patients to 2,500 lux lights for two hours/d. More recently, researchers have realized that patient compliance and acceptability are higher and efficacy seems to be about the same with a 10,000 lux light used for 30 minutes/d.

The average room lighting in a typical household ranges from 100 to 200 lux, and in the workplace it averages 200 to 400 lux. Outside light from midday sun ranges from 1,000 to 50,000 lux depending on weather conditions, distance from the equator, and time of year.

Procedure

Light boxes should be placed on a table or counter just above eye level to allow a patient's head to be within 12-18 inches of the light. Patients can work or eat while sitting under the light as long as their eyes are not shut. Patients need not look into the box, but should simply regard it as they would overhead room lighting. Sunscreen is not necessary with appropriate UV filtering.

Morning therapy generally is more effective than evening therapy.[8] Patients who do not respond to morning therapy should try evening therapy, since some patients respond to one but not the other. Light therapy works best if patients are encouraged to become active participants in their care, experimenting to establish their own personal, optimal schedule.

Response

Patients should notice a response to light therapy within 4-14 days.[7,8] This generally is faster response than is seen with selective serotonin reuptake inhibitors.[12]

Patients should continue maintenance therapy until the end of the season, since depressive symptoms often recur if light therapy is withdrawn too soon.[7] After two to four weeks, the duration of daily therapy sessions usually can be reduced by 50% without loss of efficacy.[8]

Light Boxes and Other Devices

Light boxes have emerged as the gold standard for light therapy. Good light boxes have filters to screen out UV light. UV light does not seem to contribute to the efficacy of light therapy, and it can cause significant damage to the eyes and skin.[13]

Other types of devices, such as head-mounted visors or dawn simulators, have been less well-studied.[7] Standard sun lamps should not be used for light therapy as they deliver a high content of UV light. Tanning salons are unlikely to be effective, since the tanner's eyes are covered during these sessions.

There are no data to suggest that more expensive full-spectrum lights, which provide more uniform light across the visual spectrum, offer any advantage over standard fluorescent bulbs.[13,14] This idea, and the vigorous commercial marketing that goes along with it, stems from the specialized full spectrum light that was used in the first study of light therapy. Then, researchers believed that they should try to mimic the sun's rays as closely as possible. Researchers have since realized that standard white fluorescent lights work equally well.

Light boxes are readily available on the Internet and generally cost between $200 and $600. (*See Table 1.*) Few insurers will reimburse their cost. The Society for Light Treatment and Biological Rhythms maintains a list of such companies on their web site (www.sltbr.org).

Conclusion

Light therapy appears to be safe and effective for the treatment of SAD and is the treatment of choice for this common condition.[15] Given the problems in achieving adequate placebo controls in light therapy research, however, it is difficult to assess what portion of the treatment response to light therapy derives from the placebo effect.

Recommendation

Starting in late fall, patients who suffer from winter SAD should sit in front of a UV-filtered standard fluorescent light box that is rated at 10,000 lux for 30 minutes each morning. After two to four weeks, patients can experiment by cutting back to 15 minutes each morning, continuing maintenance therapy until early spring. ❖

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Traditional Chinese Medicine and Uterine Fibroids

By Judith L. Balk, MD

TRADITIONAL CHINESE MEDICINE (TCM) INCLUDES herbal preparations, acupuncture, acupressure, qigong, oriental massage techniques, as well as other approaches.[1] Although a long tradition exists in TCM for treating gynecological problems, a MEDLINE search for all years, using all combinations of the terms myoma, leiomyoma, uterine fibroid, and hysteromyoma with acupuncture, herb, and TCM revealed only eight articles, three of which were in English. None are randomized controlled trials.

History

The earliest records of TCM use in gynecology date back to the Shang dynasty, 1500-1000 BC.[2] Bones and tortoise shells have been found with inscriptions dealing with childbirth problems, and the use of medicinal plants as a treatment for infertility was described as early as 476-221 BC.

TCM and Fibroids—Philosophy

The TCM view of physiology greatly differs from the Western perspective. In TCM, disease is caused by an imbalance or obstruction of vital energy or *qi*. Western medicine does not recognize qi, meridians, or diagnosis by imbalances of yin and yang.

In TCM, the organs have different functions than in Western medicine. For instance, in TCM, the spleen is considered to be the principal organ of digestion. It transforms food into nourishment and transports nourishment and fluid throughout the body. The spleen also is thought to govern blood and hold blood inside its proper vessels. If the spleen is deficient, blood leaks from blood vessels and manifests as petechiae, melena, hematamesis, or menorrhagia. A deficient spleen will not be able to transform food fully into nutrients and energy, and the remaining liquids and solids will accumulate and form dampness.

Pathophysiology

According to TCM, the pathophysiology of uterine fibroids is as follows: Deficient spleen energy allows dampness to accumulate. The dampness stagnates and becomes phlegm, which congeals into a tumor in the uterus, known as a uterine fibroid or leiomyoma.[3] Western medicine views the spleen markedly differently, and no connection between the spleen and leiomyomata is obvious. TCM can explain the presence of leiomyomata as the result of a deficient spleen. But can TCM treat fibroids?

Basic Science

No definitive studies have been conducted on mechanism of action. Electrical characteristics of acupuncture points differ between patients with uterine cancers and fibroids and those of control patients. A correlation between temporal parameters of electrical response of acupuncture points and the activity of uterine proliferation has been described by Russian investigators.[4]

One theory that has been suggested for acupuncture's effects on fibroids is based on the theory that regression of experimental tumor cells may be induced by local tissue destruction and repair. The authors postulated that "humoral factors at a stimulated acupoint which control and prevent local overgrowth of regenerating and proliferating cells may systemically affect the growth of distant tumors." If these humoral factors are present, and do indeed control cell growth, it is possible that a mechanism

Table 1
Ingredients in TCM tumor-resolving decoction[9]

Dong Quai (*Radix Angelicae Sinensis*)	10g
Chi Shao (*Radix Paeoniae Rubra*)	10 g
Zhe Bei Mu (*Bulbus Fritillariae Thunbergii*)	10 g
Hai Zao (*Sargasum*)	12 g
Kun Bu (*Thallus Ecloniae*)	12 g
Bie Jia (*Carapax Trionycis Preaeparata*)	12 g
Mu Li (*Concha Ostreae*)	12 g
San Leng (*Rhizoma Sparganii*)	6 g
E Zhu (*Rhizoma Zedoariae*)	6 gr

Table 2

Modifications (additions) of ingredients in TCM tumor-resolving decoction[9]

Indication	Modification (Additions to basic formula)
Blood stasis	Dan Shen (*Radix Salviae Miltiorrhizae*) and Chuan Xiong (*Rhizoma Ligustic Chuanxiong*)
Blood stasis with qi stagnation	Chuan Lian Zi (*Fructus Meliae Toosendan*) and Yuan Hu (*Rhizoma Corydalis*)
Blood stasis with qi deficiency	Dang Shen (*Radix Codonopsis Pilosulae*) and Huangqi (*Radix Astragali seu Hedysari*)
Profuse uterine bleeding with severe anemia	Buzhong Yigi Tang, Ce Bai Ye (*Cacumen Biotae*) and Di Yu (*Radix Sanguisorbae*)
After bleeding stops	Dang Shen (*Radix Codonopsis Pilosulae*) and Huangqi (*Radix Astragali seu Hedysari*)

such as this could affect fibroid growth.[5]

Some herbal products have estrogenic or antiestrogenic effects. Phytoestrogens, for instance, are plant estrogens that have both estrogen agonist and antagonist properties.[6] An estrogen antagonist could have beneficial effects on leiomyomata.

Clinical Studies—Acupuncture

No randomized controlled trials have been conducted to evaluate the effects of acupuncture on fibroids.

One case report on the use of acupuncture for fibroids and secondary infertility has been published.[5] A 35-year-old woman had large fibroids, dysmenorrhea, menorrhagia, and secondary infertility. The patient had had multiple in vitro fertilization (IVF) procedures without success, and as a last resort, accepted acupuncture treatment. The patient was treated for five weeks, twice per week, and then for 20 weeks, once per week. The size of the fibroids decreased from 12-14 weeks size to 7-8 week size, documented by ultrasound. The patient then had repeat IVF and successfully became pregnant, delivering healthy twins.

A Chinese abstract describes treating fibroids with acupuncture, with Chinese and Western medical approaches as controls.[7] The authors note that acupuncture treatment gave a "total effective rate" of 98% and a "cure rate" of 73%. Other details are unavailable.

Herbal Medicines

No randomized controlled trials of herbal approaches to fibroids have been published. However, several large case series do exist.

One Japanese case series enrolled 110 premenopausal women with fibroids less than 10 cm diameter.[8] All patients were treated with an herbal preparation of Kueichihfuling-wan (Keishi-bukuryo-gan, KBG) daily for at least 12 weeks. The average age of the subjects was 43 years old, and all patients were symptomatic from their fibroids. Hypermenorrhea and dysmenorrhea were improved in roughly 95% of all patients. Patients had ultrasounds every two weeks during the study. Fibroid size decreased in 62% of cases and increased in 4% of cases. Hormonal assays and liver function did not differ between groups.

The authors note that in young women who wish to remain fertile and in middle-aged women before menopause, KBG treatment may be a first choice as it is safe and inexpensive. However, given the lack of a control group, it is impossible to make statements on efficacy. These authors previously had reported that KBG might act as an LH-RH antagonist and a weak antiestrogen on the uterine DNA synthesis in immature rats. The combination KBG is one of the traditional Chinese herbal preparations that has been used frequently for the treatment of many gynecological disorders thought to be related to "venous congestion of pelvis." KBG is composed of five herbal drugs: cassia bark (Keihi), roots of the herbaceous peony, peach kernels, herbaceous fungus, and root bark of the peony. All patients received the same treatment.

A smaller case series enrolled 38 women with fibroids, ages 36-52, and treated each patient for three months.[9] The treatment, "Tumor-Resolving Decoction" medication, was based on TCM principles. The therapeutic principle was to "promote blood circulation, remove blood stasis, and resolve hard lumps." Basic ingredients of the decoction are shown in Table 1. The formula was individualized based on the modifications shown in Table 2. In contrast with the KBG study, treatment was individualized. The investigators followed serial ultrasounds and physical exams.

Roughly 3% of patients were cured, 42% had a marked effect on size and menstruation, 37% had improved menstruation and no change in uterine size, and 19% had no change in menstruation or fibroid size. Uterine dimensions were statistically significantly changed from before treatment to after treatment. Again, however, the lack of a control group severely limits the utility of these findings.

Diet and Lifestyle Guidelines

No published studies have evaluated the effects of a

traditional Chinese diet on leiomyoma size or growth patterns. However, dietary and lifestyle recommendations based on TCM principles for treatment of fibroids do exist.[2]

For instance, one textbook notes that patients should avoid the excessive consumption of cold-energy foods, especially cold drinks, as these tend to lead to stasis in the lower abdomen. Another recommendation is to avoid exposure to cold and dampness during the menstrual period and after childbirth. Positions for meditation and guidelines for exercise and sexual activity are also given. Those trained in Western medicine will find these recommendations to be without scientific justification. No research is published that either proves or disproves these recommendations.

There is (Western) evidence that diet may affect the risk of fibroids.[10] The diet that appears to be protective of fibroids is also a diet that is more likely to be consumed by people in Asian countries than in Western ones. For instance, an Italian case-control study found that fibroids were positively associated with intake of beef and ham. High intake of green vegetables was protective against fibroid formation. However, this study is limited by lack of an ultrasound in the control patients. A traditional Asian diet has a low intake of red meat and a relatively high intake of green and sea vegetables. However, no case-control studies report the use of a traditional Asian diet to reduce the risk of fibroids. A study of soy in American premenopausal women with fibroids is currently ongoing.

Conclusion

The data presented here are inadequate to recommend acupuncture, herbal approaches, or lifestyle approaches for treatment and prevention of uterine leiomyomata. One case-control study found that dietary differences may point to useful information, but the study design limits its utility. Prospective, randomized, and controlled trials are necessary to evaluate the effectiveness of TCM in the treatment of uterine leiomyomata.

Recommendation

TCM has a long history of treating uterine fibroids, but no adequate data exist on the efficacy. Herbal approaches are not recommended because of lack of regulation in the herbal industry and concerns about safety and contamination. Acupuncture has not been proven to be effective, and one textbook notes that uterine myomas can be dispersed only if they are very small, less than 2 cm in diameter.[2] ❖

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Reader Question

Comment: The primary problem with the article "Can Dietary Choices Prevent Prostate Cancer?" (see *Alternative Medicine Alert*, January 2001, pp. 1-5) is that it lists fat, rather than calcium, as the high risk factor for prostate cancer. While the references include some as recent as 2000 and by authors who have done some of the best research on the topic, Giovannucci and Chan, Dr. Barrette probably wrote the article based on attitudes regarding diet and prostate cancer prevalent up until a few short years ago. Now, both the cohort and ecologic approaches are in full agreement that calcium, derived from milk or other calcium sources, is the primary dietary risk factor for prostate cancer. No, the mechanism is not understood. However, the epidemiologic findings are very compelling. If the author had taken the step of going to PubMed and searching "prostate cancer diet," he would have found these references. In addition,

vitamin D and solar UVB radiation are risk reduction factors for prostate cancer, although Giovannucci has stepped back from his suggestion that calcium reduces serum vitamin D.

William B. Grant, PhD
Newport News, VA

Response: *Dr. Grant overstates his case, as two cohort studies have implicated calcium but other studies have not confirmed this. Calcium intake did appear to increase the risk of prostate cancer in men enrolled in the Health Professionals' Follow-up Study.[1] The relative risk (RR) for advanced tumors was an impressive 2.97. However, this was true for men consuming more than 2,000 mg/d of calcium—fewer than 3% of all men. The same investigators found a similar risk with calcium intake in a population-based, case-control study from Sweden.[2] However, in this study a similar RR also was seen for meat intake.*

Review of the many case-control studies of diet and prostate cancer show slightly more trials suggesting an association with meat or fat intake than with dairy or milk intake.[3] Among the cohort studies the risk of meat/fat intake is cited about as often as dairy/milk.

Three recent additional studies have not clarified this question. In a large case-control study including 697 prostate cancer cases, calcium supplement use did not increase the risk of prostate cancer.[4] A large U.S. case control with 932 prostate cancer cases found an increased risk with foods high in animal fat and no association with calcium intake.[5] A very large prospective Netherlands cohort (58,279 men, 642 prostate cancer cases) found an association with cured meats and milk but no association with calcium.[6] These three studies are much larger than almost all the prior studies.

Lastly, ecologic studies are useful in generating hypotheses but are unable to control for potential confounders.

A sensible, strongly evidence-based recommendation to our patients is to avoid a diet high in dairy and meats and low in fruits since such a diet may be associated with an increased risk of prostate cancer. This recommendation is supported by most case-control and cohort studies, and should be made by physicians to men at risk for prostate cancer.

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CME Questions

15. Chromium's role in the human body is based on its interaction with which hormone?
a. Prolactin
b. Glucagon
c. Insulin
d. Thyroxin

16. Claims that chromium picolinate supplements appear to be generally safe are based on:
a. a lack of adverse effects in clinical trials.
b. a lack of any case reports on side effects.
c. a lack of any in vitro studies raising concerns about safety.
d. all of the above

17. Which type of light source works best in the treatment of SAD?
a. Full spectrum light
b. UV light
c. Yellow-green light
d. No special light is needed; a standard fluorescent bulb works just as well.

18. What is the best light intensity to use in the treatment of SAD?
a. 10 lux
b. 300 lux
c. 10,000 lux
d. 100,000 lux

19. Which of the following therapies has been proven effective in randomized, clinical trials for treating uterine fibroids?
a. Kuei-chihfuling-wan (Keishi-bukuryo-gan, KGB)
b. Acupuncture
c. Eating a traditional Asian diet
d. All of the above
e. None of the above

With Comments from John La Puma, MD, FACP

Oolong Tea and Atopic Dermatitis

Source: Uehara M, et al. A trial of oolong tea in the management of recalcitrant atopic dermatitis. *Arch Dermatol* 2001;137:42-43.

MILD CASES OF ATOPIC DERMATITIS (AD) generally improve with standard treatment. However, standard treatment fails many patients with recalcitrant AD skin lesions. Study results in animal models have demonstrated that the administration of tea (i.e., green, black, or oolong) has suppressed type I and type IV allergic reactions. To test the effectiveness of oolong tea in the treatment of recalcitrant AD, we enrolled 121 patients; 118 patients completed the open study.

Patients were asked to maintain their dermatological treatment. However, they were also instructed to drink oolong tea made from a 10 g tea bag placed in 1,000 ml of boiling water and steeped for five minutes. This amount was then divided into three equal servings and one serving was drunk daily after three regular meals. Photographs of two or three representative lesion sites were taken at baseline and at one and six months. The severity of pruritus was assessed on a six-point Likert-like scale ranging from markedly improved (> 50% improvement) to worsened.

After one month of treatment, 74 (63%) of the 118 patients showed marked to moderate improvement of their condition. The beneficial effect was first noticed after one or two weeks of treatment. A good response to treatment was still observed in 64 patients (54%) at six months.

We conclude that the therapeutic efficacy of oolong tea in recalcitrant AD may well be the result of the anti-allergic properties of tea polyphenols.

COMMENT

Schiedermayer reports "AD is a genetically determined condition readily worsened by seasonal flare, infections, and food allergies.[1]...the only generally accepted therapy is avoiding irritants for as long as the skin is not completely healed. The benefit of topical corticosteroids is controversial.... However, clinical trials are notoriously difficult to perform, because of the inherent variability of the clinical state, the subjective nature of the assessment, and a large placebo response.[2]" (See *Alternative Medicine Alert*, January 1999, pp. 8-10).

These investigators think they have something better, and their data about oolong tea suggest just that.

There are a lot of reasons to recommend tea drinking. Oolong (made from partially fermented tea leaves, with a warm, slightly smoky flavor and burnished amber hue) can make you feel good just to drink it. Its polyphenol content is substantial. And sitting down, which one assumes most drinkers did after brewing, pouring, and while drinking, might well be an anxiolytic in itself.

The design of this trial is open label, uncontrolled, and not randomized. Yet few interventions achieve a 54% improvement in a chronic condition six months after the intervention. Particularly if the intervention is a food being used as a medicine.

Recommendation

For patients with recalcitrant atopic dermatitis, have them brew, pour, and drink oolong tea in just the way the investigators describe it above. Have them sit down when they drink, and drink slowly, as if it were effective medicine. Because it might be. ❖

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St. John's Wort Vs. Imipramine for Depression

Source: Woelk M. Comparison of St. John's wort and imipramine for treating depression: Randomised controlled trial. *BMJ* 2000;321: 536-539.

TO COMPARE THE EFFICACY AND TOLerability of *Hypericum perforatum* (St. John's wort extract) with imipramine in patients with mild-to-moderate depression, we designed a randomized, multicentre, double-blind, parallel-group trial in 40 outpatient clinics in Germany. We recruited 324 outpatients with mild-to-moderate depression and randomized them to 75 mg imipramine bid or 250 mg hypericum extract ZE 117 bid for six weeks. We used the Hamilton depression rating scale, clinical global impression scale, and patient's global impression scale as outcome measures.

Among the 157 participants taking hypericum, mean scores on the Hamilton depression scale decreased from 22.4 at baseline to 12.00 at end point; among the 167 participants taking imipramine, scores fell from 22.1 to 12.75. Mean clinical global impression scores at end point were 2.22/7 for the hypericum group and 2.42 for the imipramine group. On the seven-point self-assessments of global improvement completed by participants (1 = "very much improved;" 7 = "very much deteriorated") mean scores were 2.44 in the hypericum group and 2.60 in the imipramine group.

None of the differences between treatment groups were significant. However, the mean score on the anxiety-somatization subscale of the Hamilton scale (3.79 in the hypericum group and 4.26 in the imipramine group) indicated a significant advantage for hypericum relative to imipramine. Mean scores on the five-point scale used by participants to assess tolerability (1 = excellent tolerability; 5 = very poor tolerability) were better for hypericum (1.67) than imipramine (2.35).

Adverse events occurred in 62/157 (39%) participants taking hypericum and in 105/167 (63%) taking imipramine. Four (3%) participants taking hypericum withdrew because of adverse events compared with 26 (16%) taking imipramine.

This *Hypericum perforatum* extract is therapeutically equivalent to imipramine in treating mild-to-moderate depression, but patients tolerate hypericum better.

COMMENT

The population in which St. John's wort appears most effective is that of mildly depressed patients who are also anxious. Technically sound evidence for St. John's wort's equivalent effectiveness and better side effect profile than second-line antidepressants appears to be mounting. But the devil is in the details.

Many patients who might be candidates for St. John's wort were purposefully excluded from this trial: those pregnant, breast feeding, premenopausal, and not using contraception; those with abnormal thyroid function or other relevant abnormalities on laboratory testing; and those with bipolar disorder, previous serious psychiatric disease, or history of alcohol or drug misuse. Plus, anyone who had taken any of the following medications within the past 14 days: monoamine oxidase inhibitors, antidepressants, lithium, antipsychotic drugs, neuroleptic drugs, cimetidine, oral corticosteroids, anticonvulsants, theophylline, or thyroid hormones.

The investigators also might have added oral contraceptives, antiviral/HIV agents, and transplant medications to the list: Negating effects of all of these have been clearly documented in the peer-reviewed medical literature within the past 12 months, and summarized here. (See *Alternative Medicine Alert*, September 2000, pp. 97-101.)

Recommendation

While this extract of St. John's wort may be as effective and better tolerated than imipramine in a very narrowly defined population over the short term, St. John's wort should not be recommended—disturbing emerging reports of untoward drug interactions, especially with other medications metabolized through the cytochrome p450 pathway, are increasingly noted. ❖

Green Tea and Gastric Cancer

Source: Tsubono Y, et al. Green tea and the risk of gastric cancer in Japan. *N Engl J Med* 2001;344:632-636.

ALTHOUGH LABORATORY EXPERIments and case-control studies have suggested that the consumption of green tea provides protection against gastric cancer, few prospective studies have been performed.

In January 1984, a total of 26,311 residents in three municipalities of Miyagi Prefecture, in northern Japan (11,902 men and 14,409 women 40 years of age or older) completed a self-administered questionnaire that included questions about the frequency of consumption of green tea. During 199,748 person-years of follow-up, through December 1992, we identified 419 cases of gastric cancer (in 296 men and 123 women). We used Cox regression to estimate the relative risk of gastric cancer according to the consumption of green tea.

Green tea consumption was not associated with the risk of gastric cancer. After adjustment for sex, age, presence or absence of a history of peptic ulcer, smoking status, alcohol consumption, other dietary elements, and type of health insurance, the relative risks associated with drinking one or two, three or four, and five or more cups of green tea per day, as compared with less than one cup per day, were 1.1 (95% confidence interval [CI], 0.8 to 1.6), 1.0 (95% CI, 0.7 to 1.4), and 1.2 (95% CI, 0.9 to 1.6), respectively (P for trend = 0.13). The results were similar after the 117 cases of gastric cancer that were diagnosed in the first three years of follow-up had been excluded, with respective relative risks of 1.2 (95% CI, 0.8 to 1.8), 1.0 (95% CI, 0.7 to 1.5), and 1.4 (95% CI, 1.0 to 1.9) (P for trend = 0.07).

In a population-based, prospective cohort study in Japan, we found no association between green tea consumption and the risk of gastric cancer.

COMMENT

A prospective cohort study is better evidence than a case-control study, but not as good as an intervention study. Case-control studies have suggested that the five to 10 cups of green tea are protective against the development of gastric cancer, which remains the most prevalent cancer in Japan in both men and women. Eating salty foods increases the risk of gastric cancer; eating fruits and vegetables reduces the risk.

Green tea is made by steaming fresh tea leaves at high temperature, preserving the polyphenols that appear to be antimutagenic, anticarcinogenic, and anti-inflammatory in effect. Epigallocatechin-3-gallate is the main polyphenol in green tea. To make black tea, the same leaves are oxidized and then dried; some polyphenols remain, but green tea is supposed to have a chemoprotective effect.

In this well-done study, green tea use was confounded by varying usages of other risk and protective factors—smoking (a risk factor), pickled vegetable consumption (also a risk factor), and fruit intake (a protective factor). Nevertheless, there was no evidence of protection, even at 1 liter/d consumption, which is not uncommon in Japan. The editorialists, Takeshi Sano, MD and Mitsuru Sasako, MD of the National Cancer Center Hospital in Tokyo, report that "large cohort studies and intervention trials examining the relation between green-tea consumption and gastric cancer are under way in Japan."

Recommendation

Drink green tea for its light color, its delicate fragrance, its history, and its warming qualities. It probably does not prevent gastric cancer by itself, but certainly has other beneficial effects. ❖

In Future Issues:

Transcendental Meditation and Hypertension

Garcinia for Weight Loss

Supplement to *Alternative Medicine Alert*
April 2001

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

The B Vitamins: Part III

Vitamin B_6 (pyridoxine)

NECESSARY FOR THE PROPER FUNCTIONING OF MORE THAN 60 ENZYMES, MANY VITAMIN B_6 activities are related to the metabolism of amino acids and other protein-related compounds. Inside a cell, vitamin B_6 is phosphorylated, converting it to its active form, pyridoxal phosphate (PLP).

Dietary Reference Intakes (DRI)

0.1 mg/d for children 0-6 mo
0.3 mg/d for children 6 mo-1 y
0.5 mg/d for children 1-3 y
0.6 mg/d for children 4-8 y
1.0 mg/d for children 9-13 y
1.3 mg/d for men 14-50 y
1.7 mg/d for men 51 y and older
1.2 mg/d for women 14-18 y
1.3 mg/d for women 19-50 y
1.5 mg/d for women 51 y and older

Food Sources

Dietary sources of vitamin B_6 include brewer's yeast, wheat germ, organ meats, peanuts, legumes, potatoes, and bananas. Vitamin B_6 also is synthesized by friendly intestinal bacteria.

Mechanism of Action

- Pyridoxal phosphate is involved with amino acid metabolism, hemoglobin formation, red blood cell growth, tryptophan synthesis and conversion, and neurotransmitter production.
- Pyridoxal phosphate facilitates glycogen conversion to glucose.

Clinical Uses

- To treat hereditary sideroblastic anemia and other macrocytic anemias.
- To treat certain metabolic disorders, including xanthurenic aciduria, primary cystathioninuria, primary hyperoxaluria, and primary homocystinuria.
- To treat depression.
- To treat premenstrual syndrome, including symptoms associated with oral contraceptives.
- To treat pregnancy-induced nausea and vomiting.
- To prevent atherosclerosis by metabolizing homocysteine.
- To treat chronic fatigue syndrome.
- To correct alcohol-related B_6 deficiency.
- To prevent and treat repetitive motion injuries such as carpal tunnel syndrome.
- To relieve arthritis symptoms.
- To reduce the risk of recurring kidney stones.
- To treat seborrheic dermatitis.
- To treat children with attention deficit hyperactivity disorder.

Adverse Effects/Toxicity

- Vitamin B_6 can cause nausea, vomiting, abdominal pain, loss of appetite, headache, paresthesia, somnolence, increased serum AST, decreased serum folic acid levels, allergic reactions, breast tenderness and enlargement, and photosensitivity.
- Large doses (1-6 g/d) can be neurotoxic. Symptoms can include tingling in the hands and feet, decreased muscle coordination, and stumbling gait. Limited and inconsistent toxicity

evidence with doses of 500 mg/d. No toxicity has been reported with 100-300 mg/d; a safe upper limit is considered 100 mg/d.

Interactions/Nutrient Depletion

- Drugs that deplete vitamin B_3 include: aminoglycosides, bumetanide, cephalosporins, chlortetracycline, demeclocycline, diethylstilbestrol, doxycycline, conjugated and esterified estrogens, ethacrynic acid, fluoroquinolones, furosemide, hydralazine, hydrochlorothiazide, isoniazid, macrolides, minocycline, oral contraceptives, oxytetracycline, penicillamine, penicillins, quinestrol, raloxifene, sulfonamides, tetracyclines, theophylline, torsemide, and trimethoprim.
- Drug combinations that can deplete vitamin B_6 levels include: hydralazine and hydrochlorothiazide; hydralazine, hydrochlorothiazide, and reserpine; and hydrochlorothiazide and triamterene.
- Deficiencies manifest as dermatologic, circulatory, and neurologic disorders. Symptoms include depression, sleep disturbances, nerve inflammation, premenstrual syndrome, lethargy, decreased alertness, anemia, altered mobility, elevated homocysteine, nausea, vomiting, and seborrheic dermatitis.

Vitamin B_{12} (cobalamin)

Vitamin B_{12} is an essential growth factor that plays a role in the metabolism of cells, particularly those of the gastrointestinal tract, bone marrow, and nervous tissues. Although it is water-soluble, relatively large amounts can be stored in the liver. Vitamin B_{12} absorption is facilitated by intrinsic factor, a protein in gastric secretions, without which absorption drops to less than 1%.

Dietary Reference Intakes (DRI)

0.4 mcg/d for children 0-6 mo
0.5 mcg/d for children 6 mo-1 y
0.9 mcg/d for children 1-3 y
1.2 mcg/d for children 4-8 y
1.8 mcg/d for children 9-13 y
2.4 mcg/d for men and women 14 y and older

Food Sources

Dietary sources of vitamin B_{12} include organ meats, clams, oysters, beef, eggs, milk, chicken, and cheese.

Mechanism of Action

- Vitamin B_{12} is required for genetic code replication, myelin (the insulation around nerves) synthesis, methionine synthesis, folic acid metabolism, and red blood cells maturation.
- Vitamin B_{12} plays a role in the metabolism of protein, fat, and carbohydrates.

Clinical Uses

- To treat pernicious anemia.
- To maintain proper functioning of the nervous system.
- To prevent mouth and throat cancer in smokers.
- To relieve the symptoms of asthma.

Adverse Effects/Toxicity

Large doses of vitamin B_{12} (> 2 g/d) can be neurotoxic. Symptoms can include tingling in the hands and feet, decreased muscle coordination, and stumbling gait.

Interactions/Nutrient Depletion

- Drugs that deplete vitamin B_{12} include: aminoglycosides, cephalosporins, chlorotriansene, chlortetracycline, cholestramine resin, cimetidine, colestipol, cotrimoxazole, demeclocycline, doxycycline, famotidine, fluoroquinolones, lansoprazole, macrolides, metformin, minocycline, neomycin, nizatidine, omeprazole, oral contraceptives, oxytetracycline, penicillins, phenytoin, potassium chloride (timed release), ranitidine hydrochloride, sulfonamides, tetracyclines, trimethoprim, and zidovudine.
- Colchicine and probenecid together can deplete vitamin B_{12} levels.
- Vitamin B_{12} deficiency inhibits DNA synthesis, which affects cell growth and repair. Deficiencies manifest primarily as anemia and neurologic disorders. Symptoms include: fatigue, peripheral neuropathy, tongue and mouth irregularities, macrocytic anemia, depression, confusion, memory loss, poor blood clotting and easy bruising, dermatitis and skin sensitivity, loss of appetite, nausea, and vomiting.
- Strict vegetarians, the elderly and those with IBD, especially Crohn's disease that involves the terminal ileum, are at increased risk of deficiency.
- Intramuscular injection is the the most effective route of administration.

Resources

Dietary Reference Intakes for Thiamin, Riboflavin, Niacin, Vitamin B6, Folate, Vitamin B12, Pantothenic Acid, Biotin, and Choline. Washington, DC: National Academy Press; 1999. Available at http://books.nap.edu/books/0309065542/html/index.html. Accessed December 27, 2000.

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