ALTERNATIVE THERAPIES IN WOMEN'S HEALTH

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INSIDE

Exercise and Cardiovascular Disease

By Dónal P. O'Mathúna, PhD

EVERYONE SEEMS TO KNOW THAT SOME EXERCISE IS GOOD FOR YOU. Yet the evidence also shows that only about 20% of U.S. adults engage in the recommended amount and type of exercise, and this has not increased since the mid-1980s.[1] For those who accept the recommendation, many questions remain about how much, how often, how intense, and in what ways exercise helps. Evidence has been accumulating that exercise helps reduce the risk of Type 2 diabetes, osteoporosis, obesity, depression, and breast and colon cancer.[2] Cardiovascular disease (CVD) in particular is influenced by exercise. Since 1992, physical inactivity has been accepted as an independent risk factor for CVD.[1] Yet, CVD remains a leading killer in the United States and other developed countries. Much remains to be done to reduce CVD risk using exercise.

How Does Exercise Bring Cardiac Benefit?

The precise mechanisms by which exercise impacts CVD are not fully understood. The physiological effects of exercise are many, complex, and interrelated (see Table).[3] Physical activity has been associated with reduction in obesity, improved distribution of body fat, and lower incidence of Type 2 diabetes. Blood pressure is lower for 8-12 hours immediately after physical activity, and regular exercise results in sustained reductions in blood pressure and heart rate. Studies examining the impact of exercise on lipid profiles have had variable results, but generally show improvements. These lipid changes occur at lower exercise intensities than those needed to improve fitness. Numerous studies also show that exercise improves blood-clotting mechanisms, although much remains to be elucidated here.[4] Physical activity helps improve muscle strength, which can improve cardiac performance. Muscle blood flow is occluded during exercise, which limits cardiac ejection fraction and stroke volume, ultimately leading to improved peak cardiac performance.[3] Additionally, physical activity often leads to other beneficial lifestyle changes regarding CVD, such as smoking cessation and weight loss.

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How Much of What Sort of Exercise?

When exercise became connected with health promotion, as opposed to simply an enjoyable activity, the recommendation was to get 20 or more minutes per day of vigorous aerobic exercise such as jogging, swimming, cycling, or aerobics.[5] Since the mid-1990s, however, research has reassessed the amount and intensity of activity necessary for cardiovascular benefit. For these purposes, physical activity is defined as any bodily movement produced by skeletal muscles that results in energy expenditure.[3] Exercise is defined as those types of physical activities that are planned, structured, repetitive, and designed to improve or maintain physical fitness. Physical activity of lesser intensity is now recommended by the Centers for Disease Control and Prevention and the American College of Sports Medicine.[6] In 2003, this same recommendation was reaffirmed by the American Heart Association.[2]

This recommendation is that people engage in 30 minutes of moderate-intensity physical activity such as brisk walking on most, and preferably all, days of the week.[6] The particular type of activity does not appear to be crucial. For example, one study examined the different outcomes among 40 obese women randomized to two interventions.[7] Both groups adhered to the same weight-loss diet and had similar support groups. One group included three classes per week of vigorous step aerobics, gradually increasing from 15 to 45 minutes per class. The second group added 30 minutes per day of moderate-intensity physical activities such as walking instead of driving, or taking stairs instead of elevators. After 16 weeks and 1 year, both groups had significantly reduced body weight and CVD risk factors, such as total cholesterol, triglycerides, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and resting systolic blood pressure. Maximum oxygen uptake improved significantly in both groups. The two groups did not differ significantly in any of these measurements.

Another similar randomized controlled trial examined two exercise interventions in 235 sedentary men and women.[1] The structured exercise intervention was supervised and individually designed at a fitness center, with attendance increasing from three to five days per week. The lifestyle intervention instructed subjects on how to gradually add 30 minutes of moderately intense physical activity to most, or preferably all, days. The interventions were monitored actively for six months, with follow-up for an additional 18 months. Both groups had significantly reduced systolic and diastolic blood pressure and percent body fat, but not body weight. Cardiovascular fitness also increased. Again, the outcomes did not differ with the type of activity. Total cholesterol, LDL-C, HDL-C, and triglycerides did not change in either group, probably reflecting the lack of dietary changes. The lifestyle intervention had a mean monthly cost one-third that of the structured intervention due to fitness center costs.[8]

Exercise for People with CVD

A number of studies have shown that patients with stable chronic CVD can benefit from exercise programs.[9] Hence, over the last several years, exercise programs have become standard in cardiac rehabilitation centers. The most recent meta-analysis reported more than 50 studies in support of this trend.[10] Most of these programs were supervised for two to four months, and follow-up averaged 2.4 years. Cardiac rehabilitation programs involving only exercise reduced cardiac mortality by 31%, while more comprehensive programs involving exercise along with psychosocial and educational interventions reduced cardiac mortality by 26% (both statistically significant). However, an important limitation with this meta-analysis is that it included studies only up to 1999. Thus, many were conducted prior to widespread use of several newer pharmaceuti-

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Table

Possible biological mechanisms for exercise-induced cardiac benefits[3]

Cardiovascular influences

- Reduction of resting and exercise heart rate
- Reduction of resting and exercise blood pressure
- Reduction of myocardial oxygen demand at submaximal levels of physical activity
- Expansion of plasma volume
- Increase in myocardial contractility
- Increase in peripheral venous tone
- Favorable changes in fibrinolytic system
- Increased endothelium-dependent vasodilatation
- Increased gene expression for nitric oxide synthase
- Enhanced parasympathetic tone
- Possible increases in coronary blood flow, coronary collateral vessels, and myocardial capillary density

Metabolic influences

- Reduction of obesity
- Enhanced glucose tolerance
- Improved lipid profile

Lifestyle influences

- Decreased likelihood of smoking
- Possible reduction of stress
- Short-term reduction of appetite

cals for CVD, questioning whether the same impact would be seen in patients treated with these drugs today.

Exercise also has been shown to reduce the risk of Type 2 diabetes. People with diabetes have a very high incidence of CVD. One study examined survey data on the impact of walking on mortality among diabetic patients.[11] Compared to sedentary people with diabetes, those who walked at least two hours per week had 39% lower mortality from all causes, and 34% lower CVD mortality. Lower mortality (54%) was found for those who walked three to four hours per week, but longer duration afforded no additional benefits. Walking that led to moderate increases in heart and breathing rates gave lower mortality than walking that greatly increased these rates. The researchers estimated that one death per year could be prevented for every 61 diabetic patients who were persuaded to start walking two hours per week.

Adverse Effects

Exercise is not without its risks, although several practical steps can be taken to reduce the risk of injury. The most common type of risk in adults is musculoskeletal injury, with between one quarter and one half of adults reporting some sort of musculoskeletal injury within a year of commencing exercise.[2] The risk of injury increased with obesity, amount of exercise, and exercise intensity, especially if involving competitive sports. The risk was reduced with higher baseline fitness, supervision, stretching exercises, and wearing protective equipment such as bike helmets. Walking is a low-risk exercise where increased duration did not lead to more injuries.[12] Increasing the exercise intensity gradually resulted in fewer injuries.

Exercise also can increase risk of myocardial infarction and sudden cardiac death. A number of highly publicized deaths of high school, college, and professional athletes have drawn attention to this area. The incidence of these sudden deaths is not well documented, but is greatest in those who are least physically active and who were performing unaccustomed vigorous exercise.[2]

Recommendation

A significant body of evidence supports the cardiovascular health benefits of physical activity and exercise. Exercise has an important role in both preventing CVD and, when medically supervised, assisting in recovery from CVD. Thirty minutes of physical activity per day are recommended, although research is showing that some benefits are obtained with less activity. Therefore, people should be encouraged to gradually increase their activity by manageable amounts. This should help prevent discouragement through failing to attain overly ambitious goals or through injury. At the same time, people can be encouraged by the variety of ways they can include physical activity in their lifestyles. In the words of one researcher, "There is no single best exercise. Depending on initial fitness, health status, personal preferences, and lifestyle, any of several physical activity choices may be the right one for a given individual."[13] The important point is that people be encouraged to get active—for their heart's sake. ❖

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Current Regulations of Dietary Supplements: DSHEA Revisited

By Felise Milan, MD, and Ronit Fallek, BA

HERBAL MEDICINE CONSISTENTLY HAS BEEN FOUND TO be one of the most popular—if not the most popular—alternative therapies used in this country.[1-4] Eisenberg et al found that the use of herbal remedies increased 380% during the earlier part of the last decade (2.5% in 1990 to 12% in 1997).[2]

In 1994, the estimated market for herbal medicines was $1.6 billion annual retail sales and by 1998 that figure was up to $4 billion.[5] Since 2000, retail sales for herbal supplements have increasingly dropped each year with a fall of 13.9% in 2002.[6] This fall has been attributed to negative media coverage and medical reports about herbs, with the greatest decrement in sales seen in kava and St. John's wort, herbs that have received some of the most negative press.[7]

Current Regulation of the Herbal Industry

In 1993, the U.S. Food and Drug Administration (FDA) expressed concern about the quality and safety of vitamins, minerals, herbs, and other nutritional supplements and proposed tougher regulations governing their production and marketing. The supplement industry responded by trying to convince the public that such regulations essentially would eliminate the availability of these products from the market. In response to the flood of letters from consumers against these stricter regulations,[8] Congress passed the Dietary Supplement Health and Education Act of 1994 (DSHEA), which severely restricted the FDA's authority over these products. This federal regulation created a new category of therapeutic, non-prescription substances called "dietary supplements" (herbs, vitamins, minerals, amino acids, and other nutritional supplements) that would not be subject to premarket safety evaluations, but also could not make claims to prevent or treat disease. DSHEA allows manufacturers to make claims about a supplement's effects on the "structure and function" of the body or on the consumer's "well-being."[9] Dietary supplements must carry the disclaimer, "These statements have not been evaluated by the FDA. This product is not intended to diagnose, treat, cure, or prevent any disease." Product labels may claim that a product affects common conditions associated with "natural states," such as postmenopausal hot flashes, premenstrual moodiness, and occasional constipation.

Prior to DSHEA, supplements were regulated as foods and could not be placed on the market without FDA approval. Now, manufacturers must notify FDA within 30 days after a product is released to the public and are not required to perform any post-marketing surveillance of their product. The FDA may warn the public if it feels a product may be hazardous, but can remove the product from the market only if it proves it unsafe in a court of law, or if the director of the Department of Health and Human Services (HHS) determines the supplement to be hazardous in an administrative hearing. DSHEA proposed the creation of quality control standards, known as GMPs (Good Manufacturing Practice standards), for dietary supplements, but the industry remains without these 10 years later.

Current Problems with Dietary Supplements

In response to reports of lack of standardization, adulteration, drug interactions with, and toxicity of

herbal medicines, the medical community has voiced many concerns about herbal products. Standardization and quality control are challenging issues as the potency and constituents of any herbal product can be affected by a multitude of factors including: genetic variation; growing and harvesting conditions; storage and handling; processing and preparation; and which part of the plant is used (i.e., root, leaf, whole plant, seeds).[10]

However, several studies commissioned by consumer groups have demonstrated that herbal products sold in the United States vary widely in the concentrations of their active ingredients and that these variations are not reflected on the product label.[11] *Consumer Reports* has published studies on ginseng[8,12] that reveal variations in relevant constituents from 5% to 140% of the labeled amounts and different brands of the same herb containing up to 10 times as much as another. Several studies published in the scientific literature have found the same to be true for ephedra products.[11,13] Along with variations in active constituents, there is well-documented evidence of adulteration of herbal products made in Asia.[14] In a study conducted by the California Department of Health, 32% of the 260 products tested contained undeclared pharmaceuticals or heavy metals.[14] In February 2002, the California Department of Health ordered a recall of the product PC-SPES (a blend of Chinese herbs used to treat prostate cancer) after tests showed that it contained warfarin and diethylstilbestrol.[15]

The most serious concerns have been raised about kava (an herb used for anxiety), ephedra or ma huang (a plant-derived alkaloid used commonly for weight loss and enhanced sports performance), and St. John's wort (an herb used for mild-to-moderate depression). Kava has been associated with 25 cases of fulminant hepatitis, 11 requiring liver transplant.[16] In a review of serious adverse events from ephedra reported to the FDA from June 1997 until March 1999, the authors concluded that "dietary supplements that contain ephedra alkaloids pose a serious health risk to some users."[17] A RAND report published on ephedra found that ephedra and ephedrine were implicated in five deaths, five myocardial infarctions, 11 cerebrovascular accidents, four seizures, and eight psychiatric cases.[18] St. John's wort has been found to interfere with many medications metabolized by the liver including phenytoin, theophylline, protease inhibitors, warfarin, digoxin, and cyclosporin.[19]

Limitations of the Current Regulatory System

FDA response to reports of serious adverse effects from ephedra and kava raises questions about the ability of the federal regulatory system to adequately protect the public from unsafe dietary supplements. As mentioned previously, FDA does not have the power to prohibit the sale of dietary supplements that it considers dangerous. FDA has released warnings about ephedra and kava to which the industry has not responded. Currently, FDA is receiving comment on a proposed warning to be added to labels of all ephedra products.[20] This label would say:

> WARNING: Contains ephedrine alkaloids. Heart attack, stroke, seizure, and death have been reported after consumption of ephedrine alkaloids. Not for pregnant or breast-feeding women or persons under 18. Risk of injury can increase with dose or if used during strenuous exercise or with other products containing stimulants (including caffeine). Stop use and contact a doctor if side effects occur....[20]

Although FDA is relatively impotent in this area, the Federal Trade Commission has responded by suing several herb and supplement producers for false advertising claims.

In contrast to the lack of definitive action taken at the federal level, many U.S. states and counties have passed legislation banning the sale of any product containing ephedra. Other nations have a more closely regulated herbal industry. Kava has been banned in Australia, Canada, Switzerland, England, France, and Germany.[16] In response to reports of adulterated imported Chinese herbal products, the Japanese Ministry of Health recalled several products and now are requiring that chemical analyses be done on all Chinese herbs imported into Japan.[21]

As a result of the reports of adverse effects and adulterated products, both the medical community and federal agencies are calling for increased regulation of dietary supplements. Members of the medical community have identified the current state of dietary supplement regulation as posing a serious threat to public health, and proposed new legislative action that would entail the restoration of jurisdiction to government agencies to monitor and regulate dietary supplements both pre- and postmarketing, and more strict legislation and accountability for supplement manufacturers.[21,22] These specific recommendations include: GMPs modeled after those for drugs; premarket product testing; mandatory postmarketing surveillance, adverse event reporting, and registration with the FDA of every company producing dietary supplements; non-misleading advertisements; clear and accurate labeling with both botanical and common plant names, adverse effect information, and potential herb-drug interactions.[21,22]

Current Proposals on Supplement Regulation

A decade after DSHEA was passed, several additional legislative actions have been proposed and are pending. In

March 2003, FDA submitted a new proposal to the *Federal Register* for industry-wide dietary supplement GMPs and labeling requirements. Both industry and non-industry factions are concerned that FDA's proposed GMP guidelines inappropriately align dietary supplements with pharmaceutical drugs, as opposed to foods, leading to overly stringent manufacturing and surveillance requirements. FDA currently is accepting comments on the proposal and soon will finalize the guidelines.

Another current controversy over dietary supplement regulation surrounds the proposed Dietary Supplement Safety Act of 2003 (DSSA),[23] introduced by Sen. Dick Durbin (D-IL) in the Senate in March 2003, and which adopts many of the medical community's recommendations. This bill would mandate dietary supplement manufacturers and distributors to register with and receive premarketing approval from FDA; to conduct post-marketing surveillance; and to investigate, monitor, and report on serious adverse effects to the HHS. It authorizes the HHS secretary to discontinue the marketing of a product if its investigation finds it to be unsafe; prohibits the introduction of unapproved stimulants; and shifts the burden of proof of dietary supplement risk from the FDA to the manufacturers. The dietary supplement industry is resisting these legislative efforts, perceiving them as excessive and restrictive.

Another bill, the DSHEA Full Implementation and Enforcement Act of 2003 (DFIEA), introduced by Sen. Tom Harkin (D-IA) and Sen. Orrin Hatch (R-UT) (the authors of DSHEA), proposes to uphold DSHEA and to increase FDA's budget to implement DSHEA from $9.7 million in 2003 to $65 million by 2008.[24] The senators maintain that the current problems in product safety have resulted not from a problem with DSHEA, but from FDA's failure to enforce the bill, due primarily to a lack of funds.

As they did in 1993, industry factions are encouraging consumers to write to Congress in protest of DSSA and in support of DFIEA, under the premises that increased regulation will severely restrict the public's access to products.

However, a recent survey on views of dietary supplement regulation indicates that a majority of Americans favor increased governmental regulation, provided that this would not deny consumer access to products that have been tested for safety. Eighty-one percent of respondents supported premarketing approval by FDA for new supplements; 80% supported FDA's authority to remove products from the market when proven unsafe; and a majority of respondents supported increased governmental regulation to ensure that products are unadulterated, accurately advertised, and contain standardized doses.[25]

Conclusion

Many patients are using herbs and dietary supplements. The data tell us that these products vary significantly in their quality and safety. The scientific literature reflects the concern of the medical community at large that the current regulatory environment does not adequately protect patients from potential harm. Significant changes are needed to increase the regulatory power and action of the federal government over the dietary supplement industry. The public seems to agree. It will be important for us to follow these developments, as they are likely to have a significant impact on our patients' safety and health. ❖

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CE Objectives

After reading *Alternative Therapies in Women's Health*, the health care professional will be able to:

1. evaluate alternative medicine and complementary therapies for women's health concerns;

2. identify risks and interactions associated with alternative therapies;

3. discuss alternative medicine options with patients; and

4. offer guidance to patients based on the latest science and clinical studies regarding alternative and complementary therapies.

CE/CME Instructions

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

CE / CME Questions

22. The Centers for Disease Control and the American College of Sports Medicine recommend that people engage in how many minutes per day of moderate-intensity physical activity most days of the week?

a. 20
b. 30
c. 45
d. 60

23. What cardiovascular risk factors are positively affected by increased physical exercise?

a. Total cholesterol
b. Low-density and high-density cholesterol
c. Resting systolic blood pressure
d. All of the above

24. The Dietary Supplement Health and Education Act of 1994 gave the U.S. Food and Drug Administration more authority over the regulation of herbs, vitamins, minerals, amino acids and other nutritional supplements.

a. True
b. False

25. Serious safety concerns have been raised about:

a. kava
b. ephedra
c. St. John's wort
d. All of the above

Answers: 22. b, 23. d, 24. b, 25. d.

Government funding studies on CAM for cancer prevention and treatment

The National Center for Complementary and Alternative Medicine (NCCAM) in Bethesda, MD, recently announced several research studies that are focusing on CAM for cancer prevention and treatment. These studies may also look at whether CAM therapies may interfere with or enhance conventional treatments.

The studies come at a time when interest in CAM therapies among adults with cancer is high. The NCCAM Clearinghouse, which responds to inquiries about CAM from the public, receives more questions about CAM therapies for cancer than for any other medical condition.

One survey places the percentage of adult cancer patients who use CAM at 83%, NCCAM says. Among the CAM approaches used by cancer patients include prayer, meditation, and other forms of spiritual practice; vitamins, herbs, and special diets; exercise and other movement therapies; imagery and other relaxation techniques; and traditional Chinese medicine.

NCCAM specifically funds rigorous studies on CAM through grants to researchers at leading centers around the country and in its own Division of Intramural Research. In fiscal year 2002, NCCAM's expenditures for cancer research totaled $14,253,000, or 16% of its research portfolio. In addition, NCCAM collaborates with other National Institutes of Health (NIH) institutes and centers, especially the National Cancer Institute.

The centers in the NCCAM research portfolio go through the same competitive application process as other NIH grants, says Michelle Bolek, MPH, a NCCAM spokesperson. "Federal code specifies this process and it is uniform across government agencies. The center grants are currently funded for three to five years with each subsequent year's funding dependent on progress."

An integral part of NCCAM's research portfolio is its network of specialized centers of research. (For more information, see www.nccam.nih.gov/training/centers.) Two centers currently are focusing on cancer research.

The Johns Hopkins Center for Cancer Complementary Medicine in Baltimore, MD. Researchers at Johns Hopkins, led by principal investigator Adrian S. Dobs, MD, are studying CAM modalities for cancer, including the antioxidant effects of herbs in cancer cells; the antioxidant and anti-inflammatory properties of soy and tart cherry on aspects of cancer pain in four animal models; and the impact of spiritual practices on disease recurrence and immune and neuroendocrine function in African-American women with breast cancer.

The Specialized Center of Research in Hyperbaric Oxygen Therapy at the University of Pennsylvania in Philadelphia. The research, led by principal investigator Stephen R. Thom, MD, PhD, is conducting four projects to examine the mechanisms of action, safety, and clinical efficacy of hyperbaric oxygen therapy for head and neck tumors. The center is developing and validating a model to predict who benefits from hyperbaric oxygen benefits after laryngectomy; examining the effects of hyperbaric oxygen on growth of blood vessels and tumors; characterizing the effects of hyperbaric oxygen on cell adhesion and growth of metastatic tumor cells in the lung; and testing the effects of elevated oxygen pressures on cellular levels of nitric oxide.

Two centers have cancer research as a part of their research portfolios.

The Botanical Center for Age-Related Diseases at Purdue University in West Lafayette, IN. This research, led by Connie M. Weaver, PhD, is studying the health effects of plant polyphenols. Examples of these include soy, grapes, green tea, and several herbs. The Purdue researchers are collaborating with investigators at the University of Alabama at Birmingham (UAB). Stephen Barnes, PhD, is directing the UAB research.

The Center for Dietary Supplements Research on Botanicals at the University of California, Los Angeles. The center, led by David Heber, MD, PhD, is conducting basic and clinical research to explore the potential mechanisms of action of yeast-fermented rice for cholesterol reduction. It is examining the implications for heart disease prevention of green tea extract and soy for inhibition of tumor growth.

These four centers are conducting clinical trials with human volunteers and preclinical research, which does not involve human subjects, Bolek says.

The NCCAM Division of Intramural Research's Oncology Program also is investigating selected CAM therapies for cancer. Currently, the division is conducting studies of:

Electroacupuncture, for delayed nausea and vomiting from chemotherapy in pediatric patients with osteosarcoma. Electroacupuncture, a variation of traditional acupuncture, involves placing needles on selected points on the body and pulsing them with an electric current to stimulate the points.

The herb mistletoe, combined with the chemotherapy drug gemcitabine, for patients with pancreatic, colorectal, lung, or breast cancer. Data from early studies suggest that mistletoe, either alone or in combination with chemotherapy, may stimulate the immune system and help cancer patients to feel better overall.

More information on NCCAM-sponsored clinical trials is available at nccam.nih.gov/clinicaltrials. ❖

In Future Issues:

Vitamin C and CHD Protection for Women
Valerian for Insomnia

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ANNUAL FINANCIAL DISCLOSURE STATEMENTS

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