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Dietary Supplements and Health: Need, Benefit and Safety Concern

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INTRODUCTION

Research to determine the impact of nutrient-containing dietary supplements on nutritional and health status has been undertaken for many years, and considerable preclinical evidence (from *in vitro* laboratory research to *in vivo* animal studies) exists for many essential nutrients. Many epidemiologic studies from various parts of the world have focused on the possible relationships between specific nutrient intakes and prevalence and severity of chronic diseases. Small clinical studies related to chronic disease also have been conducted for several micronutrients and human safety data are available. The growth in the field of dietary supplement research is evident from the increase in federal spending within the past decade. In 1995 the Office of Dietary Supplements (ODS) at the National Institutes of Health was budgeted to receive just less than $1 million to support dietary supplement research compared with $26 million in 2004 (1). The expanded budget has allowed for a significant increase in the breadth and depth of the research conducted; it is this knowledge base that will be used to inform consumers, health care practitioners, and health policy makers in their recommendations about the use of dietary supplements for people in various stages of life.

Data from the latest National Health and Nutrition Examination Survey (NHANES) indicate that 52% of the U.S. adults were taking a least one dietary supplement in 1999~2000, most commonly a multivitamin and multimineral supplement (35%) (2). Market data show that in 2003 the sale of vitamins, herbs and botanicals, sports nutrition supplements, minerals, meal supplements, and other specialty supplements totaled $19.82 billion, representing a $3.37 billion (20.5%) increase since 1999 (3). The 2003 sales of vitamins and minerals, in either a multivitamin-multimineral or single-nutrient form, were 42% of all sales ($8.41 billion).

Data from NHANES and other research efforts have also been useful in identifying characteristics of the primary users of supplements and the reasons for supplement use. Higher usage of dietary supplements is generally associated with being female, having an education beyond high school, having a higher income, being non-Hispanic white, and being older. The most recent NHANES data indicate that although an increase in the use of supplements may have occurred, no evidence suggests shifts in usage patterns among the different demographic groups.

Reasons cited for usage of dietary supplements by various subgroups suggest that a large segment of people living in the United States is adopting a health promotion strategy that includes seeking alternative forms of medicine, including the use of dietary supplements. Supplements are used to improve nutrition, make up for nutrients missing in the food supply, decrease susceptibility to or severity of disease, increase energy (vitality), or improve performance. Herbal and botanical preparations are frequently used to supplement conventional medical treatments.

The passage of the 1994 Dietary Supplement Health and Education Act (DSHEA) also played a role in increasing the use of supplements in the United States by ensuring consumer access to a wide range of dietary supplements (4). The Food and Drug Administration (FDA) has authority to regulate dietary supplements under

authority of the Federal Food Drug and Cosmetic Act. As an amendment to this act, DSHEA defines a dietary supplement as a product (other than tobacco) intended to supplement the diet that contains one or more of certain dietary ingredients, such as a vitamin, a mineral, an herb or other botanical substance, or an amino acid. Products may not be presented as conventional foods but instead are available in capsules, tablets, etc. Manufacturers are required to have evidence to support their claims of efficacy and safety but are not required to seek approval of their claims by FDA before marketing except under certain rare circumstances. FDA was required to institute good manufacturing practices to govern the production of dietary supplement products; as of this writing, these regulations are still in a public comment period before enactment.

DSHEA also created a vehicle for developing a broader knowledge base on the supplements being used by authorizing the creation of ODS. The mission of ODS is to strengthen knowledge and understanding of dietary supplements by evaluating scientific information, stimulating and supporting research, disseminating research results, and educating the public to foster an enhanced quality of life and health for the U.S. population.

The ODS provides research funding through collaboration with the NIH Institutes and Centers (ICs) in support of basic and clinical studies addressing dietary supplements. Through this process, grant applications that are reviewed through the standard NIH review process and fall within the research priority areas of the ODS, can be submitted to the ODS for co-funding. ODS also uses other available mechanisms (such as cooperative agreements, interagency agreements and contracts) to meet its goals. The ODS has several program areas: a) evidence-based reviews of efficacy and safety of dietary supplements that ODS and its IC partners use to define target areas for future research; b) a program of dietary supplement research centers focused on botanicals, in collaboration with NCCAM, NIEHS, and other ICs and Offices; c) collaboration with ICs on intervention studies that use specific well-defined dietary supplements, including botanicals, as major variables; d) a training and career development program for the preparation of scientists in a variety of disciplines to address emerging problems of dietary supplement research; e) databases of dietary supplement ingredients, developed in collaboration with other Federal agencies, to support surveys of dietary supplement intake and exposure; f) analytical methods and reference materials program; and g) consumer-oriented products, including Fact Sheets, databases of dietary supplement research activities and literature citations.

This paper presents a summary of the evidence available on the need, benefits, and safety concerns of nutrient-containing dietary supplement use throughout the life cycle (5), followed by a discussion on the use of evidence-based reviews to develop a future research agenda (1). The dietary supplements selected for review in this paper include those for which there is ample evidence. The evidence presented is categorized according to life cycle stage: infancy (birth through 12 months), childhood (1 year through 18 years), adulthood, and older adulthood (70 years of age and older). Although these categories do not reflect all the variations in physiological growth and status that are seen throughout the life cycle, they do represent categorical differences that are applied for the development of recommended intakes for essential nutrients and evaluating the effect of supplemental amounts.

The Efficacy of Nutrient Dietary Supplements Through the Lifecycle

Evaluation of evidence related to the effects of dietary supplements on nutrition and health must take into account the effect of a person's stage of life and general health status on the absorption, utility, and need for a particular constituent of dietary supplements. Physiological needs for specific nutrients, and consequently their anticipated effects, differ at various stages in the life cycle. At any stage of life, genetic profile and lifestyle behaviors also will influence an individual's response to supplemental intake of the nutrient under investigation.

The development of research on dietary supplements must take into account physical development, general health status, and physiological changes specific to each nutrient at each stage of life. What is beneficial in one situation may have no effect or a negative affect in another situation. For example, a systematic review of the evidence from epidemiologic studies and randomized controlled trials of vitamin supplementation to prevent either cancer or cardiovascular disease (CVD) was conducted by the U.S. Preventive Services Task Force in 2003. The conclusion of the task force was that findings did not demonstrate a consistent or significant effect of any single vitamin or combination of vitamins on either incidence of or death from CVD. The task force concluded that beta-carotene supplements, alone and in combinations, appeared to harm those at risk for lung cancer although not the general population.

Infants

Iron Iron plays a key role in human life as a component of a number of proteins including hemoglobin which is critical for the transport of oxygen and electrons to tissues throughout the body. Healthy full term infants are born with a supply of iron that lasts for 4 to 6 months. Iron in human milk is well absorbed by infants. It is estimated that infants can use about 50% of the iron in human milk compared to less than 12% in infant formula. The American Academy of Pediatrics (AAP) recommends that infants be exclusively breast fed for about the first six months of life. Gradual introduction of iron-enriched foods should complement human milk from 7 to 12 months of age. Infants weaned from human milk before 12 months of age should receive iron-fortified infant formula (6). Iron supplementation is not recommended because of the availability of iron fortified foods targeted for this age group.

Vitamin D Vitamin D's major biological function is to maintain serum calcium and phosphorus concentrations within the normal range by enhancing the efficiency of the small intestine to absorb these minerals from the diet. In infants, vitamin D requirements cannot be met by human milk alone. Sunlight is a potential source of vitamin D for infants, but the AAP advises that infants be kept out of direct sunlight and wear protective clothing and sunscreen when exposed to sunlight. Therefore, AAP recommends a daily supplement of 200 IU vitamin D for breastfed infants beginning within the first 2 months of life unless they are weaned to receive at least 500 mL (about 2 cups) per day of vitamin D-fortified formula (7). Formula fed infants usually consume recommended amounts of vitamin D because the 1980 Infant Formula Act requires that infant formulas be fortified with a minimum of 40 IU vitamin D per 100 calories of formula.

Children

Calcium Childhood is a time of critical growth and development with adequate calcium intake being essential for bone mass development. Dietary calcium has been associated not only with the development of increased peak bone mass but also with reduced bone loss later in life. During the development of peak bone mass, calcium intakes of less than 1000 mg per day are associated with reduced bone mineral density (8). Data indicate that on average, only children under age 8 years are meeting their recommended calcium intake. Although it is best to get as much calcium as possible from foodsbecause calcium-rich foods also provide nutrients involved in calcium utilizationcalcium supplementation may be appropriate for children who do not eat calcium-rich foods (9).

Adults

Vitamin E Vitamin E, a fat-soluble vitamin consisting of tocopherols and tocotrienols, functions as an antioxidant, promoting normal formation of red blood cells and normal function of the nervous and immune systems. Naturally found in vegetable, nut, and seed oils, the average vitamin E intake is sufficient to prevent signs of deficiency.

However, it is one of the most commonly consumed supplements, which may reflect its postulated role in decreasing the risk of CVD, prostate cancer, and various other chronic diseases. However, evidence of a role of vitamin E in the prevention of these diseases is mixed. Several large clinical studies are currently being conducted that will help to clarify the role of vitamin E. Four large clinical trials are currently studying the effect of vitamin E supplements alone or combined with other antioxidants. These include the Women's Health Study, Women's Antioxidant and Cardiovascular Study, Physicians' Health Study II, and Heart Protection.

The Prostate Cancer Prevention Trial is a double-blind, placebo-controlled trial of a drug for the primary prevention of prostate cancer. Because 35% of the study population regularly took vitamin E supplements, the final results will include analyses of the interactions between this and other supplements and the treatment. The Selenium and Vitamin E Prevention Trial (SELECT) is expected to help clarify the association of dietary supplement use with prostate and other cancers. SELECT is a randomized, prospective, double-blind study designed to determine whether selenium and vitamin E reduce the risk of prostate cancer in healthy men.

Selenium Selenium is a nonmetallic trace mineral with biological functions including defense against oxidative stress, regulation of thyroid hormone action, and regulation of redox status of vitamin C and other molecules (10). In the U.S., most cases of selenium depletion or deficiency are associated with severe gastrointestinal problems, such as Crohn's disease, or with surgical removal of part of the stomach. These and other gastrointestinal disorders can impair selenium absorption, potentially leading to the need for supplementation.

While some studies indicate that mortality (death) from cancer, including lung, colorectal, and prostate cancers, is lower among people with higher blood selenium levels or intake, not all studies showed a relationship between selenium status and cancer. These conflicting results emphasize the need for additional research on the relationship between selenium and chronic diseases such as cancer. A study that may help answer some of the questions about the effect of selenium supplementation on cancer risk is the French SU.VI.MAX study. This prevention trial provides doses of antioxidant vitamins and minerals that are one to three times higher than recommended intakes, including a daily supplement of 100 g selenium. More than 12,000 men and women are being followed for 8 years to determine the effect of supplementation on the incidence of chronic diseases, such as cancers and CVD.

The SELECT study, as mentioned above, also is investigating the relationship between selenium and prostate cancer in healthy men. A daily supplement containing 200 µg of selenium will be given to individuals in the selenium-only study group, while men in the combined-nutrients group will receive a daily supplement containing 200 µg selenium and 400 mg vitamin E.

Folate Folate (including the naturally occurring forms found in foods as well as folic acid, the synthetic form, in fortified foods and dietary supplements) participates as a coenzyme in reactions that require the transfer of a single carbon in the metabolism of nucleic and amino acids. The need for folate supplementation for adults focuses on two different groups: women capable of becoming pregnant and middle-aged and older adults.

Neural tube defects are the most common major congenital malformation of the central nervous system. They result from a disturbance of the embryonic process of neurulation, which is initiated approximately 21 days after fertilization and is completed by 28 days of gestation. Neurulation therefore may begin before a woman realizes that she is pregnant. Epidemiologic studies and nonrandomized and randomized clinical trials have indicated a significant decrease in risk of NTD with increasing dietary folate (11). The recommended intake for women capable of becoming pregnant is 400 µg per day from supplements and dietary intake. Folate intake continues to be important during pregnancy. When folate intake is inadequate, maternal serum and erythrocyte folate concen-

trations decrease and megaloblastic marrow changes may occur resulting in megaloblastic anemia (11). Several studies confirm that folic acid consumed in conjunction with diet prevents folate deficiency in pregnant women. The Recommended Dietary Allowance for folic acid during pregnancy is 600 μg per day, a level of intake difficult to achieve from a normal mixed diet (12). In response to the overwhelming evidence of the effect of folic acid on the reduction of risk of NTDs, the Centers for Disease Control, in 1992, recommended that all women who could become pregnant should take a daily 400 μg folic acid supplement as a preventative measure. Subsequently, the FDA issued a regulation requiring all enriched grain products to be fortified with folic acid (140 μg per 100 g) in 1996, adding an estimated 100 μg folic acid to the average diet of American women.

A deficiency of folate, vitamin B-12, or vitamin B-6 may increase the blood level of homocysteine, which is derived from the intracellular metabolism of methionine. Evidence shows that an elevated homocysteine level is an independent risk factor for CVD and stroke. Plasma homocysteine is increased in patients with coronary, cerebral, or peripheral arterial diseases. Such associations of homocysteine with arterial occlusive diseases were documented in retrospective, cross-sectional, and prospective studies. However, no evidence indicates that lowering homocysteine with supplemental vitamins will reduce CVD risk. Randomized placebo-controlled trials are in progress to determine whether supplementation with folic acid, vitamin B-12, or vitamin B-6 can lower the risk of developing CVD.

It is important that older adults be aware of the relationship between folic acid and vitamin B-12 because of their greater risk of having a vitamin B-12 deficiency. Some concern exists that supplemental folic acid could mask the signs of vitamin B-12 deficiency. Folic acid supplements can correct the anemia associated with vitamin B-12 deficiency, its key diagnostic sign. Unfortunately, folic acid cannot correct the permanent nerve change that is possible if vitamin B-12 deficiency is not treated. Intake of supplemental folic acid should not exceed 1000 g per day to prevent folic acid from masking symptoms of vitamin B-12 deficiency (11).

Elderly

Vitamin B-12 Vitamin B-12 (cyanocobalamin) is essential for proper brain and nerve development, DNA synthesis, and DNA methylation. Dietary vitamin B-12 must be separated from food proteins before the vitamin can be bound to intrinsic factor, the complex in which it is absorbed in the small intestine. In elderly people with atrophic gastritis and low stomach acids, separation of vitamin B-12 from proteins in food and its binding to intrinsic factor can be impaired. To maintain adequate plasma values of vitamin B-12, elderly adults with this condition should consume sources of unbound vitamin B-12 such as found in supplements or food that has been fortified with the vitamin.

Vitamin D More than 50% of free-living and institutionalized elderly have been reported to have low circulating levels of vitamin D. Vitamin D deficiency causes abnormalities in calcium and bone metabolism resulting in secondary hyperthyroidism, osteomalacia, and exacerbated osteoporosis (13). Older Americans are thought to have a higher risk of developing vitamin D deficiency given the decreasing ability of their skin convert vitamin D to its active form. Additionally, the kidneys, which help to convert vitamin D to its active form, sometimes do not function as well when people age. Vitamin D insufficiency, which occurs often in post-menopausal women and older Americans, is associated with greater incidence bone loss. Because bone loss increases the risk of fractures, vitamin D supplementation may help prevent fractures resulting from osteoporosis.

Calcium Adequate calcium intake is also required to maintain bone mineral density and reduce the risk for osteoporosis in the elderly. In addition to reduced absorption of calcium by elderly people that results from age-related changes in vitamin D metabolism, the elderly also show a reduced ability to increase the efficiency of

calcium absorption as an adaptive response to low-calcium diets. As indicated previously, low-acid stomach conditions are highly prevalent among the elderly and can also reduce calcium absorption. Dietary calcium reacts with hydrochloric acid to form soluble calcium chloride, which can be absorbed in the small intestine. In the United States the recommended calcium intake is 1200 mg per day for men and women older than age 70 years. Many elderly individuals may need dietary supplements to achieve this recommended intake.

CONCLUSIONS

The preceding summary indicates the possible needs for and benefits to be derived from the use of dietary supplements in various stages of life. The body of this evidence is increasing but still not comprehensive enough to serve as a basis for public health recommendations. Formal systematic reviews are continuously needed to fully evaluate the existing literature and to identify research gaps and promising approaches. The hierarchy of evidence needed to substantiate the impact of supplement use begins with preclinical and epidemiologic evidence. Although these lines of evidence may provide insight into anticipated outcomes, it is important that research be taken to the next level of clinical trials. Before the conduct of human clinical trials, all available evidence must be reviewed thoroughly and objectively to determine whether the evidence on efficacy and safety justify proceeding to clinical trials. Such evidence-based systematic reviews differ from traditional opinion-based narrative reviews in that they systematically attempt to reduce bias by the comprehensiveness and reproducibility of the search for and selection of articles for review. Systematic reviews also assess the methodological quality of the included studies and evaluate the overall strength of the body of evidence (14). When the body of evidence on safety and efficacy justifies proceeding to clinical trials, the trials are usually conducted in three phases: human safety trials, small efficacy trials (usually in defined target groups), and large-scale trials that are essential in moving from basic and observational science to evidence-based public health recommendations.

The Office of Dietary Supplements (ODS) at NIH developed an evidence-based review program, using the Agency for Healthcare Research and Quality (AHRQ) Evidence-Based Practice Center program to conduct systematic reviews of the scientific literature. ODS uses these reviews to help NIH establish research agendas for dietary supplements. An example of a recent review is that of omega-3 fatty acids.

In late October 2002, ODS commissioned evidence-based review on the health benefits of omega-3 fatty acids. Working with eight NIH institutes, ODS developed a set of questions on the relationship between omega-3 fatty acids consumption and cardiovascular disease, cancer, child and maternal health, asthma, gastrointestinal conditions, renal conditions, transplantation, autoimmune disorders, eye diseases, neurological disorders, and mental health.

Systematic reviews of the available literature found evidence that long chain omega-3 fatty acids, the beneficial component ingested by eating fish or taking a fish oil supplement, reduce heart attack and other problems related to heart and blood vessel disease in persons who already have these conditions, as well as their overall risk of death. Although omega-3 fatty acids do not alter total cholesterol, HDL cholesterol, or LDL cholesterol, evidence suggests that they can reduce levels of triglyceridesa fat in the blood that may contribute to heart disease. The review also found other evidence indicating that fish oil can help lower high blood pressure slightly, may reduce risk of coronary artery re-blockage after angioplasty, may increase exercise capability among patients with clogged arteries, and may possibly reduce the risk of irregular heart beatsparticularly in individuals with a recent heart attack. Findings from the first 5 evidence reviews on omega-3 fatty acids were published in March, 2004 (http://www.ahrq.gov/clinic/epcindex.htm#dietsup). An additional six reviews on will be issued in 2005 and available at

the same website.

ODS continues to work with NIH Institutes and Centers to nominate topics for ODS evidence-based reviews. Nominations are ranked according using criteria such as the following: 1) knowledge from existing science or the risks and benefits, including controversies or uncertainties, about the effectiveness or safety; and, 2) availability of scientific data to support the systematic review and analysis of the topic in regard to a) impact on prevalence, incidence, and mortality of condition/disease; b) potential to improve condition/disease/safety outcomes; c) potential to improve consumer/patient/provider decision-making; d) availability of research resources/organizations to address the results of the topic review; e) whether or not the topic is already being addressed by ongoing NIH research programs; f) Congressional interest; and, g) consumer interest.

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