Wednesday, 3:00 – 4:30, F6

The Safety and Efficacy of Vitamin Supplements

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Objectives:

Identify effective methods for the practical application of concepts related to improving the delivery of services for persons with developmental disabilities

Notes:

Safety and Efficacy of Vitamins, Minerals, and Dietary Supplements

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2017

Supplements

Pros	Cons
• _____	• _____
• _____	• _____
• _____	• _____
• _____	• _____

What is a Dietary Supplement?

Dietary Supplement Regulation

- Dietary Supplement Health and Education Act of 1994
  - Definition of dietary supplement*
  - "…..not evaluated by the FDA. ….not intended to diagnose, treat, cure, or prevent….."
  - Remove product only when hazardous

Definition of Dietary Supplement

- Product intended to supplement the diet
- Intended for ingestion in pill, capsule, tablet, or liquid
- Not considered a food
- Not considered a drug
- Labeled as "dietary supplement"

Dietary Supplements

- Vitamins/Minerals
- Essential fatty acids
- Enzymes/coenzymes (ex. Coenzyme Q10)
- Plant-derived (Herbs)
- Animal-derived (ex. Glucosamine)
- Bacteria (ex. Lactobacilli acidophilus)
- Glandular products (ex. Adrenal extracts)
- Hormonal (ex. Melatonin)

Supplements

Pros

- _____
- _____
- _____
- _____

Cons

- _____
- _____
- _____
- _____

Advantages Regarding Supplements

- Patient autonomy
- No prescription necessary
- Cheaper than prescription medication
- Profit to be made?

2000 National Health and Nutrition Examination Survey

Am J Epidemiol 2004;160:339-349

- 52% adults reported taking a dietary supplement in the past month
- 35% reported taking a multivitamin/mineral supplement in past month
- 2007 dietary supplement sales = $23.7 billion
  - Multivitamins = $4.5 billion

Advantages Regarding Supplements

- Vitamins for malnutrition
  - Only 3-4% Americans meet the recommended micronutrient intake via food

Factors for Inadequate Intake

- Elderly persons
- Smokers
- Nursing home patients
- Teenagers
- Alcoholics
- Pregnancy
- Breastfeeding

Inadequate Intake

- Vegetarians
- Picky eaters
- Insufficient money/food
- Certain diseases
  - Cystic fibrosis
  - GI conditions
  - Bariatric surgery
  - Anorexia

Limitations to Supplements

- Polypharmacy
- Potentially unsafe
- Cost
- Absence of FDA approval
- Lack of reputable manufacturers
- Quality of products

Potentially unsafe

- Estimated 23,000 ER visits/year in US
- Due to
  - Side effects
  - Drug interactions
  - Larger doses than recommended

Potentially unsafe

- Side effects
  - Many supplements increase risk of bleeding
    - Some examples: Vitamin A, Vitamin E, Selenium, Ginkgo, Green tea extract
- Recommendation
  - Preoperative recommendations about using or stopping dietary supplements
  - 2-3 weeks before elective surgery

Potentially unsafe

- Drug interactions
  - Ginkgo and aspirin
  - Ginseng and blood pressure medicine
  - Valerian and sedatives
  - St. John's wort

St. John's Wort

- Drug Interactions (P450 1A2, 2C9, 2C19, 3A4)
  - Antidepressants (serotonin syndrome)
    - Paroxetine, sertraline, nefazodone
  - Anti-retrovirals (decreased effect)
    - Protease inhibitors, NNRTI
  - Barbiturates (decreased levels)
  - Clopidogrel (increased efficacy)

St. John's Wort

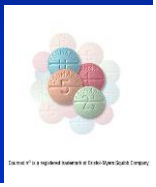
- Drug Interactions (P450 1A2, 2C9, 2C19, 3A4)
  - Cyclosporine (decreased levels)
  - Digoxin (decreased levels)
  - Irinotecan and Imatinib (decreased efficacy)
  - Methadone (decreased efficacy)
  - Methylphenidate (decreased efficacy)

St. John's Wort

- Drug Interactions (P450 1A2, 2C9, 2C19, 3A4)
  - Narcotics (increased sedation)
  - Omeprazole (decreased efficacy)
  - Oral Contraceptives (decreased efficacy)
  - Phenytoin (decreased efficacy)
  - Statins (decreased efficacy)
  - Tacrolimus (decreased efficacy

St. John's Wort

- Drug Interactions (P450 1A2, 2C9, 2C19, 3A4)
  - Theophylline (decreased levels)
  - ?Triptans?
  - Tramadol
  - Warfarin (decreased INR)



Potentially unsafe

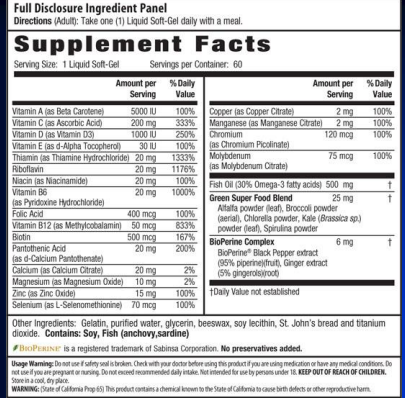
- Larger doses than recommended
  - Vitamin A
  - Vitamin B6

Vitamin A

- Toxicity
  - Stored in liver daily, daily supple is usually not necessary
  - High doses of carotenoids do not usually produce toxicity
  - Toxicity has been reported in adults taking > 25,000 IUs daily for several years
  - Symptoms include:
    - » Dry itchy skin, bone pain, anorexia, diarrhea, birth defects, brittle nails, gingivitis, fatigue, increased infections, hair loss, headaches, enlarged liver, abnormal liver function
    - » Birth defects: face, head, brain, heart

Vitamin B6

- RDI: 1.3-1.5 mg/day
- Toxicity
  - Upper Tolerable Limit: 100 mg
  - Toxic: 250 mg
- Well absorbed in the upper portion of the small intestine: acidic environment increases the amount of vitamin B_6 absorbed



Full Disclosure Ingredient Panel
Directions (Adult): Take one (1) Liquid Soft-Gel daily with a meal.

Supplement Facts

Serving Size: 1 Liquid Soft-Gel Servings per Container: 60

	Amount per Serving	% Daily Value
Vitamin A (as Beta Carotene)	5000 IU	100%
Vitamin C (as Ascorbic Acid)	200 mg	333%
Vitamin D (as Vitamin D3)	1000 IU	250%
Vitamin E (as d-Alpha Tocopherol)	30 IU	100%
Thiamin (as Thiamine Hydrochloride)	20 mg	1333%
Riboflavin	20 mg	1176%
Niacin (as Niacinamide)	20 mg	100%
Vitamin B6 (as Pyridoxine Hydrochloride)	20 mg	1000%
Folic Acid	400 mcg	100%
Vitamin B12 (as Methylcobalamin)	50 mcg	833%
Biotin	500 mcg	167%
Pantothenic Acid (as d-Calcium Pantothenate)	20 mg	200%
Calcium (as Calcium Citrate)	20 mg	2%
Magnesium (as Magnesium Oxide)	10 mg	2%
Zinc (as Zinc Oxide)	15 mg	100%
Selenium (as L-Selenomethionine)	70 mcg	100%
Copper (as Copper Citrate)	2 mg	100%
Manganese (as Manganese Citrate)	2 mg	100%
Chromium (as Chromium Picolinate)	120 mcg	100%
Molybdenum (as Molybdenum Citrate)	75 mcg	100%
Fish Oil (30% Omega-3 fatty acids)	500 mg	†
Green Super Food Blend Alfalfa powder (leaf), Broccoli powder (aerial), Chlorella powder, Kale (*Brassica sp.*) powder (leaf), Spirulina powder	25 mg	†
BioPerine Complex BioPerine® Black Pepper extract (95% piperine)(fruit), Ginger extract (5% gingerols)(root)	6 mg	†

†Daily Value not established

Other Ingredients: Gelatin, purified water, glycerin, beeswax, soy lecithin, St. John's bread and titanium dioxide. **Contains: Soy, Fish (anchovy,sardine)**

BioPerine® is a registered trademark of Sabinsa Corporation. **No preservatives added.**

Usage Warning: Do not use if safety seal is broken. Check with your doctor before using this product if you are using medication or have any medical conditions. Do not use if you are pregnant or nursing. Do not exceed recommended daily intake. Not intended for use by persons under 18. **KEEP OUT OF REACH OF CHILDREN.** Store in a cool, dry place.
WARNING: (State of California Prop 65) This product contains a chemical known to the State of California to cause birth defects or other reproductive harm.

STRESS B COMPLEX

Serving Size 2 Capsules
Servings Per Container 30

Amount Per Serving		% Daily Value
Vitamin C (as ascorbic acid)	1g	1670%
Thiamin (as thiamin hydrochloride)	50 mg	3330%
Riboflavin	50 mg	2940%
Niacin (as niacinamide)	100 mg	500%
Vitamin B_6 (as pyridoxine hydrochloride)	50 mg	2500%
Folic Acid	400 mcg	100%
Vitamin B_{12} (as cyanocobalamin)	250 mcg	4170%
Biotin	100 mcg	35%
Pantothenic Acid (as d-calcium pantothenate)	250 mg	2500
Inositol	100 mg	†
PABA (as para-aminobenzoic acid)	50 mg	†
Choline (as choline bitartrate)	40 mg	†

† Daily Value not established.

OTHER INGREDIENTS: Gelatin, Magnesium Stearate, Silica.

Unsafe Dietary Supplements

Food and Drug Administration

- Carcinogens
  - Borage*
  - Calamus
  - Coltsfoot
  - Comfrey*
  - Life root
  - Sassafras

Unsafe Dietary Supplements

Food and Drug Administration

- Hepatotoxicity
  - Butterbur*
  - Chaparral
  - Germander
  - Life root
  - Pennyroyal oil → renal/ hepatic
  - Heliotrope
  - Comfrey
  - Kava*

Unsafe Dietary Supplements

Food and Drug Administration

- Miscellaneous
  - Licorice* → pseudoaldosteronism
  - Ma Huang (ephedra) → death
  - Pokeroot (Children)
  - Willow bark
  - Jin Bu Huan → paralysis
  - Stephania and Magnolia → kidney failure

Unsafe Dietary Supplements

Food and Drug Administration

- Miscellaneous
  - Germanium → acute renal failure
  - Lobelia → respiratory depression and death
  - L-tryptophan or Phenylalanine → eosinophilia-myalgia syndrome
  - Yohimbe* → seizures and death

12 Dangerous Dietary Supplements Named by Consumer Reports

http://www.drugdanger.com/Others/4-04-01consumerreports.htm

- Androstenedione
- Aristolochic Acid (cancer)
- Bitter orange
- Chaparral
- Comfrey
- Germander
- Kava
- Lobelia (tachycardia)
- Organ/glandular products
- Pennyroyal (liver/kidney)
- Skullcap (liver damage)
- Yohimbe

Quality of Supplements

Pediatrics 2008;121:775-781

- Brands of dietary supplement products not equivalent
- Lack of active ingredient consistency
- Difficulty in identifying reputable manufacturers

FDA Regulation on Supplements

- FDA does not regulate
  - Standardization
  - Efficacy
  - Safety
  - Drug interactions

Standardization

ConsumerLab.com

Complete List of Product Reviews (alphabetical)

A-C	D-J	K-P	R-Z
5-HTP (5-Hydroxytryptophan)	Dark Chocolate and Cocoa (Flavanols)	Kefir	Red Clover Isoflavones
7-Keto DHEA	DHA	Krill Oil (Omega-3)	Red Yeast Rice
Acai Berry	DHEA	L-Theanine	Resveratrol
Acetyl-L-Carnitine	Diet Powders/Drinks	Lactase Supplements	Rhodiola
Acidophilus	Digestive Enzymes	Lactobacillus	SAMe
African Mango	Echinacea	Lactose-Free Milk	Saw Palmetto
ALA (alpha-linolenic acid)	Energy Bars	Leucine	Selenium
Algal Oil (Omega-3)	Energy Drinks	Lutein	Sexual Enhancers
Aloe	EPA	Lycopene	Soy Isoflavones
Alpha Lipoic Acid	Epimedium (horny goat weed)	Lysine (L-lysine)	St. John's Wort
Amino Acid Combinations	Evening Primrose Oil	Maca	Sterols
Arginine (L-arginine)	Eye Health Supplements	Magnesium	Stimulant Blends
Ashwagandha	Fiber Supplements (Webinar)	Mangosteen	Theanine
B Vitamins & Complexes	Fiber Bars	Matcha Green Tea	Thiamin
Baobab	Fish Oil (DHA & EPA)	Meal Replacement & Food Bars	Toprol (Drug)
Beta-Carotene	Fish Oil (Omega-3) for Pets	Meal Replacement Powders/Drinks	Tryptophan (L-Tryptophan)
Beta-sitosterol (for cholesterol)	Flaxseed Oil	Melatonin	Turmeric
Beta-sitosterol (for prostate)	Folic Acid	Memory Enhancers	Ubiquinol
Bifidobacterium	Garcinia cambogia (HCA)	Menopause Supplements	Valerian
Bilberry		Melatonin (Drug)	Vision Supplements

USP Verification

http://www.usp.org/USPVerified/

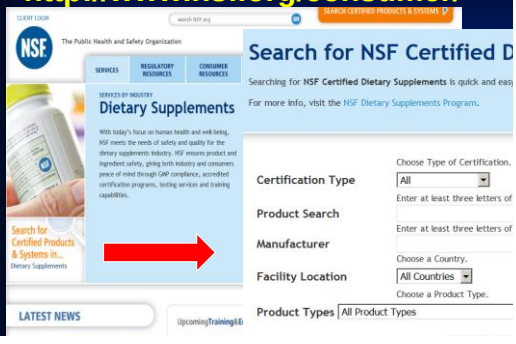
USP Verified

Find USP Verified Dietary Supplements

Visit the links below to view USP Verified products and the locations where you can find them.

Nature Made	• Products • Where to Buy	KIRKLAND Signature	• Products • Where to Buy
TruNature®	• Products • Where to Buy	Berkley & Jensen	• Products • Where to Buy

National Science Foundation
http://www.nsf.org/consumer/



Who Should Take Vitamins/minerals?

- Age 65 or older
- Postmenopausal Women
- Poor dieters/ very low calorie diets/picky eaters
- Smokers
- Alcoholics
- Pregnant Women
- Impaired Absorption

Directions: Adults: One tablet daily, with food.

Supplement Facts

Serving Size: One tablet

	Amount Per Serving	% Daily Value		Amount Per Serving	% Daily Value
Vitamin A (20% as beta-carotene)	2500 IU	50%	Vitamin B_{12}	6 mcg	100%
Vitamin C	60 mg	100%	Biotin	300 mcg	100%
Vitamin D (as Vitamin D_3)	1000 IU	250%	Pantothenic Acid	10 mg	100%
Vitamin E	22.5 IU	75%	Calcium (elemental)	500 mg	50%
Vitamin K	25 mcg	31%	Iron	18 mg	100%
Thiamin (B_1)	1.5 mg	100%	Iodine	150 mcg	100%
Riboflavin (B_2)	1.7 mg	100%	Zinc	15 mg	100%
Niacin	20 mg	100%	Selenium	20 mcg	29%
Vitamin B_6	2 mg	100%	Copper	2 mg	100%
Folic Acid	400 mcg	100%	Manganese	2 mg	100%
			Chromium	120 mg	100%

INGREDIENTS: Calcium Carbonate, Microcrystalline Cellulose, Ascorbic Acid, Ferrous Fumarate, Less than 2% of: Beta-Carotene, Biotin, Cholecalciferol, Chromium Chloride, Croscarmellose Sodium, Cupric Oxide, Cyanocobalamin, D-Calcium Pantothenate, dl-Alpha-Tocopheryl Acetate, FD&C Blue #2 Lake, FD&C Yellow #5 (tartrazine) Lake, FD&C Yellow #6 Lake, Folic Acid, Hydroxypropyl Methylcellulose, Magnesium Oxide, Manganese Sulfate, Niacinamide, Phytonadione, Polyethylene Glycol, Potassium Iodide, Pyridoxine Hydrochloride, Riboflavin, Silicon Dioxide, Sodium Selenite, Stearic Acid, Thiamine Mononitrate, Titanium Dioxide (color), Vitamin A Acetate, Zinc Oxide.

WARNING: Accidental overdose of iron-containing products is a leading cause of fatal poisoning in children under 6. Keep this product out of reach of children. In case of accidental overdose, call a doctor or poison control center immediately.

A COMPLETE MULTIVITAMIN WITH MORE OF WHAT MATTERS TO WOMEN

One A Day® Women's is a complete multivitamin specially formulated for women. It contains 100% daily value of all 8 B-Vitamins†, which help convert food to energy, and 5 other essential nutrients.†*

†Refers to Daily Values for Vitamins B_1, B_2, B_6, B_{12}, Niacin, Folic Acid, Biotin and Pantothenic Acid.
‡Refers to Vitamin C, Copper, Manganese, Chromium and Iron.

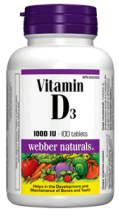
*This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.

Who is at risk for Vitamin D deficiency?

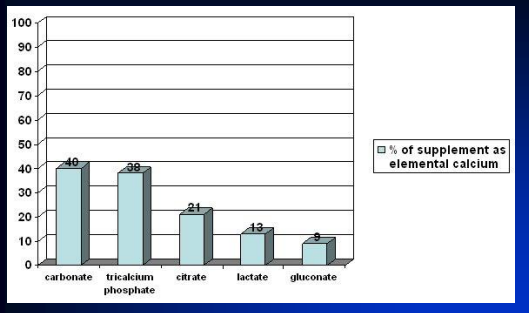
- People who live in smoggy/overcast areas
- People who live and work primarily indoors
- Dark-skinned people
- >50 years old

Vitamin D

- 800-1000 IU/day in healthy adults
- Some may require higher doses
  - 25-OH Vitamin D level
    - » Normal = 30-75 ng/mL
    - » Insufficient = 20-29
    - » Deficient = < 20



Calcium Products



http://ods.od.nih.gov/factsheets/Calcium_pf.asp

Calcium Products

- Must be soluble and ionized for absorption
  - Acidic pH increases solubility
  - Vitamin D also necessary
- Insoluble salts should be taken with food
  - Calcium carbonate, phosphates, "shell" products

Calcium Administration

- Individual doses >500 mg will not be absorbed
  - Use BID or TID schedule
- Vitamin D 400-1,000 IU/day advised to ensure absorption

Supplement Facts

Serving Size: 1 Tablet

	Amount Per Serving	% Daily Value
Calcium (Carbonate)	500 mg	50%
Vitamin D (Cholecalciferol)	250 IU	63%

* Daily Value not established

Other Ingredients: Vegetable stearic acid, aqueous film coating (purified water, hydroxypropyl methylcellulose and vegetable glycerine), vegetable magnesium stearate, croscarmellose sodium, microcrystalline cellulose and silicon sioxide.

General Guidelines Regarding Dietary Supplements

- Pregnancy, lactation
- Children
- Medications
  - Warfarin
  - Metabolized by liver
- Immunocompromised states
  - Cancer, HIV, transplant patients
- Anti-obesity supplements
  - Laxatives, diuretics, ma huang, thyroid herbs

Information Resources

- **Efficacy and Safety**
  - **Office of Dietary Supplements, National Institutes of Health**
- **Quality Products**
  - **USP Verification**

Supplement Facts

Serving Size 1 tablet

	Amount Per Serving	% Daily Value
Vitamin A (50% as beta carotene)	3500 IU	70%
Vitamin C	60 mg	100%
Vitamin D	800 IU	200%
Vitamin E	30 IU	100%
Thiamin	1.5 mg	100%
Riboflavin	1.7 mg	100%
Niacin	20 mg	100%
Vitamin B6	2 mg	100%
Folic Acid	400 mcg	100%
Vitamin B12	6 mcg	100%
Biotin	30 mcg	10%
Pantothenic Acid	10 mg	100%

	Amount Per Serving	% Daily Value
Calcium	200 mg	20%
Iron	18 mg	100%
Phosphorus	20 mg	2%
Iodine	150 mcg	100%
Magnesium	50 mg	13%
Zinc	11 mg	73%
Selenium	55 mcg	79%
Copper	1 mg	50%
Chromium	35 mcg	29%
Chloride	72 mg	2%
Potassium	80 mg	2%
Boron	75 mcg	†
Vanadium	10 mcg	†
Silicon	2 mg	†

†Daily Value not established.

Position of the American Dietetic Association: Nutrient Supplementation

ABSTRACT

It is the position of the American Dietetic Association that the best nutrition-based strategy for promoting optimal health and reducing the risk of chronic disease is to wisely choose a wide variety of nutrient-rich foods. Additional nutrients from supplements can help some people meet their nutrition needs as specified by science-based nutrition standards such as the Dietary Reference Intakes. The use of dietary supplements in general, and nutrient supplements in particular, is prevalent and growing in the United States, with about one third of adults using a multivitamin and mineral supplement regularly. Consumers may not be well informed about the safety and efficacy of supplements and some may have difficulty interpreting product labels. The expertise of dietetics practitioners is needed to help educate consumers on the safe and appropriate selection and use of nutrient supplements to optimize health. Dietetics practitioners should position themselves as the first source of information on nutrient supplementation. To accomplish this, they must keep up to date on the efficacy and safety of nutrient supplements and the regulatory issues that affect the use of these products. This position paper aims to increase awareness of the current issues relevant to nutrient supplements and the resources available to assist dietetics practitioners in evaluating the potential benefits and adverse outcomes regarding their use.

J Am Diet Assoc. 2009;109: 2073-2085.

0002-8223/09/10912-0013$36.00/0
doi: 10.1016/j.jada.2009.10.020

POSITION STATEMENT

It is the position of the American Dietetic Association that the best nutrition-based strategy for promoting optimal health and reducing the risk of chronic disease is to wisely choose a wide variety of foods. Additional nutrients from supplements can help some people meet their nutrition needs as specified by science-based nutrition standards such as the Dietary Reference Intakes.

The focus of this American Dietetic Association (ADA) position paper is the use of nutrient supplements, particularly vitamin and mineral supplements, in assisting people in meeting their nutrient needs. Fortified food, a topic previously included within this ADA position paper, is discussed in ADA's position paper on functional foods (1). Other nutrients such as fatty acids (2) and fiber (3) are also discussed in separate ADA position papers. Supplementation of non-nutrient ingredients is covered in ADA's practice paper on dietary supplements (4).

The use of dietary supplements in general and nutrient supplements in particular is prevalent and growing in the United States. Based on the 1999-2000 National Health and Nutrition Examination Survey, 52% of adults reported taking a dietary supplement in the past month and 35% said they took a multivitamin/mineral supplement (MVM) (5). Adults who used MVM supplements most often included women, older adults, non-Hispanic whites, people with more than a high-school education, people who rate their health as excellent/very good, and under- and normal-weight people (5). Supplements of vitamin E, vitamin C, calcium, and B-complex vitamins were used by at least 5% of adults. In the 1999-2004 National Health and Nutrition Examination Survey, 34% of children and adolescents reported supplementing their diets with some type of vitamin and mineral supplement (6). Factors associated with greater use among children included younger age, more healthful diets, greater food security, greater physical activity, and better access to health care (6).

In 2007, dietary supplement sales grew to $23.7 billion (7). Sales of multivitamins, the most commonly pur-

This American Dietetic Association (ADA) position paper includes the authors' independent review of the literature in addition to systematic review conducted using ADA's Evidence Analysis Process and information from ADA's Evidence Analysis Library (EAL). Topics from the EAL are clearly delineated. The use of an evidence-based approach provides important added benefits to earlier review methods. The major advantage of the approach is the more rigorous standardization of review criteria, which minimizes the likelihood of reviewer bias and increases the ease with which disparate articles may be compared. For a detailed description of the methods used in the Evidence Analysis Process, go to http://adaeal.com/eaprocess/. Evidence-based information for this and other topics can be found on the EAL at www.adaevidencelibrary.com and subscriptions for nonmembers are purchasable at www.adaevidencelibrary.com/store.cfm.).

Conclusion statements are assigned a grade by an expert work group based on the systematic analysis and evaluation of the supporting research evidence. Grade I=Good; Grade II=Fair; Grade III=Limited; Grade IV=Expert Opinion Only; and Grade V=Not Assignable (because there is no evidence to support or refute the conclusion).

chased of supplements, grew 3.9% in 2007 to $4.5 billion in sales for the year. Sales of single-nutrient supplements, including calcium, B vitamins, vitamin C, vitamin A/beta carotene, magnesium, and iron also grew during this period, whereas vitamin E supplement sales declined slightly (7). Contributing to this industry's growth are the aging of the population and consumer desire to maintain good health and prevent disease.

Although many Americans use dietary supplements, a 2009 report from the US Government Accountability Office stated that "according to experts, consumers are not well-informed about the safety and efficacy of dietary supplements and have difficulty interpreting labels on these products" (8). The Government Accountability Office expressed concern that the uninformed use of dietary supplements may expose consumers to health risks (8). The expertise of dietetics practitioners is needed to help educate consumers on safe and appropriate selection and use of dietary supplements, including nutrient supplements. The primary objective of this paper is to increase awareness of the current issues relevant to nutrient supplements and the resources available to assist dietetics practitioners in evaluating the potential benefits and adverse outcomes regarding their use.

DEFINITION AND REGULATORY FRAMEWORK

Nutrient supplements, like other dietary supplements, are regulated as a subcategory of food by the Food and Drug Administration's (FDA's) Center for Food Safety and Applied Nutrition. The Dietary Supplement Health and Education Act of 1994 (DSHEA) (9), which amended the Federal Food, Drug, and Cosmetic Act of 1938, defines and sets safety and labeling requirements for dietary supplements. The DSHEA defines a dietary supplement, in part, as a product intended to supplement the diet that contains any of the following dietary ingredients: a vitamin; a mineral; an herb or other botanical; an amino acid; a dietary substance for use by humans to supplement the diet by increasing the total dietary intake; or a concentrate, metabolite, a constituent, extract, or combination of any ingredient mentioned above (9). Dietary supplements are intended to be taken by mouth and can be in many forms, including pills, capsules, tablets, liquids, powders, or other forms as long as they are not represented for use as a conventional food or as a sole item of a meal or diet (9). They must also be identified on the label as a dietary supplement (9).

Label Claims

Dietary supplement labels can bear health claims (authorized and qualified), nutrient content claims, and structure/function claims (10). Health claims can be used to characterize the relationship between a dietary ingredient and reducing the risk of a disease or health-related condition (10). Nutrient content claims can be used to characterize the amount of a nutrient (10). Both health claims and nutrient content claims must be preapproved by the FDA. Structure/function claims are the most commonly used claims on dietary supplement labels (4). They can be used to describe the following: the effect a dietary ingredient has on the structure or function of the body; the way a dietary ingredient acts to maintain a structure or function; general well-being from consumption of a dietary ingredient; or a benefit related to a nutrient deficiency disease if the prevalence of the disease in the United States is also indicated (10). Structure/function claims are not preapproved by the FDA. The manufacturer is responsible for ensuring the claims they make are truthful and not misleading and must provide the FDA with the text of structure/functions claims no later than 30 days after marketing the supplement (10). Labels that contain structure/function claims must also carry the disclaimer that explains to the consumer that the FDA has not evaluated the label claim and that the product is not intended to "diagnose, treat, cure, or prevent any disease" (10). Although the FDA has the primary responsibility of claims on product labeling, the Federal Trade Commission has the responsibility of regulating claims made in the advertising of dietary supplements (11).

Safety

Manufacturers are responsible for ensuring their products are safe before they put them on the market (12). Vitamins and minerals were sold as ingredients in dietary supplements before DSHEA was implemented and are, therefore, presumed to be safe based on their history of use. They do not require an FDA premarket review of safety or efficacy (12). For any new dietary ingredient (sold after DSHEA was passed) and not recognized as a food substance present in the food supply, the manufacturer (and distributor) must provide notification to the FDA of their intention to market the product and provide them with the information they used to conclude the ingredient was generally safe to consume (12-14). Once marketed, the FDA has the authority to remove a product if they prove it to be unsafe (12). The FDA monitors safety, in large part, by collecting reports on adverse events from consumers, health professionals, and manufacturers through their MedWatch program—The FDA Safety Information and Adverse Event Reporting Program (15). Reporting adverse events associated with a dietary supplement was voluntary for manufacturers until new legislation, the Dietary Supplement and Nonprescription Drug Consumer Protection Act (16), went into effect December 22, 2007. The new regulation requires the responsible party (ie, the manufacturer, packer, or distributor whose name appears on the label) to submit Serious Adverse Event Reports to the FDA within 15 business days of receiving a report and to maintain records of all adverse event reports for 6 years (17). Reporting of events not considered serious remains voluntary. Adverse events are considered serious if they result in death, a life-threatening experience, inpatient hospitalization, a persistent or significant disability or incapacity, or a congenital anomaly or birth defect; or require, based on reasonable medical judgment, a medical or surgical intervention to prevent an outcome listed above (18). The submission of an adverse event report is not an admission by the company that the product involved caused or contributed to the adverse event (17).

According to a 2009 Government Accountability Office report, the num-

ber of all adverse event reports received increased threefold after mandatory reporting went into effect compared to the previous year, but underreporting remains a concern (8). From December 2007 through October 2008, the FDA received 596 mandatory serious adverse event reports (8). Of these reports, 66% were associated with combination products and products that did not fall under any of the available categories, 40% with vitamins, and 19% with minerals (8). The percentages total more than 100% because reports that involved more than one product were counted in more than one category. No causal relationships between adverse events and the associated products could be made, in part, because of the variability in the quality and detail of the information provided in the reports (8).

Quality

In June 2007, the FDA, with authority granted under DSHEA, published a final rule establishing current Good Manufacturing Practices for dietary supplements (19). This rule establishes regulations that require the consistent manufacturing of products with regard to identity, purity, strength, and composition (20). Companies are responsible for ensuring their products meet quality standards, including being accurately labeled (eg, products contain the ingredients in the amounts stated on their labels) and free from contaminants (eg, bacteria, pesticides, glass, lead, and other heavy metals) and foreign materials (19). The requirements are being phased-in over a 3-year period depending on the company size. All companies are expected to be in compliance by June 2010 (19).

Independent organizations such as ConsumerLab.com (a for-profit company), NSF International, and US Pharmacopoeia offer programs that evaluate supplement quality (21-23). Each organization has, at a minimum, a program that allows manufacturers, if they choose, to pay a fee to have their products tested; those that conform to the organization's quality specifications can bear that organization's seal of approval on their label. The absence of a seal does not in and of itself indicate inferior quality. High costs to analyze for each ingredient may be one factor that limits some companies, particularly smaller companies, from having their products tested.

OPTIMAL INTAKES

Nutrient-Based Recommendations

Optimal nutrient intakes are those that promote health and reduce risk for chronic disease while minimizing risk of excess. The Institute of Medicine's (IOM's) Dietary Reference Intakes (DRIs) are the best available evidence-based nutrient standards for estimating optimal intakes. They include the Recommended Dietary Allowances (RDAs), Adequate Intakes (AIs), Estimated Average Requirements (EARs), and Tolerable Upper Intake Levels (ULs) (24).

The RDAs and AIs (when data was not sufficient to determine an EAR and thus an RDA) serve as intake goals for healthy individuals. These levels may not be adequate to replete individuals who are malnourished (24). In addition, levels higher, or lower, than recommended levels may be necessary to meet the needs of people with specific health conditions or who take medications that alter their requirement for a nutrient (24). The recommended intakes can be used as goals for nutrients not affected by the condition or medication; estimates of other nutrients should be based on best evidence for the circumstance such as provided in hospital diet manuals and from professional organizations (24). The recommended intake values and the endpoints on which the values were established have been summarized in the IOM's *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements* (25).

The UL is the "maximum level of daily nutrient intake that is likely to pose no risk of adverse effects" (26). It was determined there was a need for ULs because of increased intakes of nutrients from fortified foods and dietary supplements (25). The ULs for vitamin E, niacin, and folate apply only to synthetic forms of the nutrients as is found in supplements and fortified foods (26). The UL for magnesium applies to intakes from pharmacological agents only (26). The UL for vitamin A is from preformed vitamin A or retinol only (26). For all other nutrients, ULs apply to total intake from food, water, and supplements. For nutrients for which data were insufficient to determine a UL (ie, biotin, carotenoids, pantothenic acid, riboflavin, thiamin, vitamin B-12, vitamin K) the IOM warns that caution may be warranted in consuming levels above the RDAs and AIs (26). See the Figure for IOM Web sites that provide the UL values and the adverse effects of excess consumption associated with each nutrient.

DRI Updates. Experts have suggested the DRIs for vitamin D be updated based on evidence accumulated since the 1997 release. Although consensus has not been reached, some experts indicate that the recommended intake should be increased to 1,000 IU/day for all adults (27) and the UL be increased from 2,000 IU to 10,000 IU (28). The desirable blood concentration for optimal vitamin D status has also been debated. According to some experts, advantages begin at a 25-hydroxyvitamin D (25[OH]D) concentration of 75 nmol/L (30 ng/mL), whereas between 90 and 100 nmol/L (36 to 40 ng/mL) is ideal for a variety of endpoints (27). An IOM committee is currently assessing the relevant data to update the DRIs for vitamin D and calcium as they find appropriate (29). The report is scheduled to be released by May 2010.

The American Academy of Pediatrics (AAP) released updated vitamin D recommendations in 2008. Recommendations for healthy infants and children were increased from a minimum of 200 IU per day beginning in the first 2 months after birth to a minimum of 400 IU per day beginning soon after birth to prevent rickets and vitamin D deficiency (30). The AAP recommends serum 25(OH)D concentrations of 50 nmol/L (20 ng/mL) in infants and children (30). These recommendations as they pertain to supplementation are further discussed in the "Nutrient Supplements in Practice" section.

Using DRIs to Assess Total Nutrient Intakes. The DRIs are used to assess adequate and excess nutrient intakes and plan diets for groups and individuals. Dietary assessment information can be used to help dietetics practitioners determine if an individual is likely to benefit from or is at risk for excess intakes from taking dietary supplements and in appropriate product selection.

When an individual's usual intake

Web Sites		
Organization	**URL**	**Contents**
Agency for Healthcare Research and Quality (AHRQ)	www.ahrq.gov/clinic/epcindex.htm#dietsup	• AHRQ produced evidence-based reviews on nutrient supplements
American Dietetic Association	www.eatright.org	• Position papers • Practice paper on dietary supplements • Evidence Analysis Library • Other documents: Guidelines Regarding the Recommendation and Sale of Dietary Supplements, Code of Ethics for the Profession of Dietetics
Cochrane Collaboration	www.cochrane.org/reviews/	• Free access to abstracts and links to full reviews of evidence-based health care topics including vitamins and minerals used for disease prevention and treatment
Food and Drug Administration	www.fda.gov/Food/DietarySupplements/default.htm	• Dietary supplement alerts and safety information • Adverse event reporting • Guidance, compliance, and regulatory information • Other documents: Tips for the Savvy Supplement User: Making Informed Decisions and Evaluating Information, Tips for the Older Dietary Supplement Users
Institute of Medicine	*Elements:* www.iom.edu/Object.File/Master/7/294/0.pdf *Electrolytes and water:* www.iom.edu/Object.File/Master/20/004/0.pdf *Vitamins:* www.iom.edu/Object.File/Master/7/296/webtablevitamins.pdf	• Tables that include Dietary Reference Intake values and adverse effects of excessive consumption
Micronutrient Information Center, Linus Pauling Institute, Oregon State University	lpi.orst.edu/infocenter	• Evidence-based monographs on vitamins, minerals, other nutrients, and dietary phytochemicals that include information on nutrient function, deficiency symptoms, interactions, recommended intakes, supplements, and safety
National Agricultural Library	www.nal.usda.gov/fnic/pubs/bibs/gen/dietarysupplementsprofessionals08.pdf	• Dietary Supplements: Resources for Professionals (January 2008) • Listing of resources (bibliographies/databases, books/book chapters, newsletters, Web resources, agencies and organizations) providing technical and professional-level information on dietary supplements including nutrition information
National Library of Medicine	dietarysupplements.nlm.nih.gov/dietary www.nlm.nih.gov/medlineplus/vitaminandmineralsupplements.html	• The Dietary Supplements Labels Database (DSID)—Information about label ingredients in >3,000 selected brands of dietary supplements • MedlinePlus for Vitamin and Mineral Supplements
Office of Dietary Supplements, National Institutes of Health (NIH)	ods.od.nih.gov	• International Bibliographic Information on Dietary Supplements (IBIDS) Database—Published, scientific literature on dietary supplements including vitamins, minerals, and botanicals • Expert reviewed Facts Sheets on vitamins, minerals and botanicals that include information on medication interactions and signs and symptoms of deficiency and toxicity • Computer Access to Research on Dietary Supplements (CARDS)—Database of federally-funded research projects pertaining to dietary supplements.
Therapeutic Research Center	www.naturaldatabase.com	• Natural Medicines Comprehensive Database (subscription required)—Includes evidence-based monographs that contain information on ingredient safety, effectiveness, adverse reactions and interactions
US Department of Agriculture, Agricultural Research Service, Office of Dietary Supplements, NIH, and other federal agencies	dietarysupplementdatabase.usda.nih.gov/	• Dietary Supplement Ingredient Databases (DSID)—Estimates levels of ingredients in dietary supplement products

Books

Coates PM, Blackman MR, Cragg GM, Levine M, Moss J, White JD. *Encyclopedia of Dietary Supplements,* New York, NY: Marcel Dekker; 2005.
Fragakis AS, Thomson CA. *The Health Professional's Guide to Popular Dietary Supplements.* 3rd ed. Chicago, IL: American Dietetic Association; 2006.
Hendler S, Rorvik D, eds. *PDR for Nutritional Supplements.* 2nd ed. Montvale, NJ: Thomson Reuters; 2008.
Institute of Medicine. *Dietary Reference Intakes: The Essential Guide to Nutrient Requirements.* Washington, DC: National Academies Press; 2006.

Figure. Resources for information related to dietary supplements.

meets or exceeds recommended levels, it is likely that their intake is adequate; that is, they are likely to be consuming an amount of a nutrient needed to maintain the specific adequacy endpoint for which the value was derived. This is because RDAs meet or exceed the estimated requirement of all but 2% to 3% of the population, and AIs represent intakes likely to exceed the actual requirements of almost all healthy people (24). For the same reason, usual intakes that fall below recommended levels should not be interpreted as inadequate (24). Clinical status and biochemical indexes should be among the factors included with intake data to assess an individual's dietary adequacy and nutritional status (24). The totality of information should be used to determine if a person is likely to benefit from nutrient supplementation. The UL is an important tool that dietetics practitioners can use to assist consumers in the safe use of dietary supplements. As average daily intakes exceed the UL, the risk of adverse health effects increases (24).

It is important to note that when comparing a person's intake to DRIs to assess adequacy, one is actually assessing apparent adequacy because an individual's true requirement and true intake of a nutrient are not known (24). Day-to-day variability in intakes and limitations in methods of collecting intake data and nutrient databases all affect intake estimates, and various factors including genetics affect true nutrient requirements. The IOM published *Dietary Reference Intakes: Applications in Dietary Assessment* (24) to provide guidance on using the DRIs to assess intakes.

Food-Based Recommendations

Wise selection of nutrient-rich foods is generally the best strategy for meeting nutrient needs. Foods, particularly plant foods such as fruits, vegetables, whole grains, beans, nuts, seeds, and teas, provide an array of other health-promoting substances beyond vitamins and minerals, including carotenoids and polyphenols such as flavonoids. Data suggest that positive health outcomes are related more to dietary patterns, the types and amounts of foods consumed, than to intakes of individual nutrients (31).

The US Department of Health and Human Services and the US Department of Agriculture's 2005 Dietary Guidelines for Americans (DGA) provide guidance on diet and physical activity to promote health and decrease the risk of chronic disease (32). The DGA will be revised in 2010. MyPyramid provides recommended food intake patterns for 12 energy levels that range from 1,000 to 3,200 kcal per day (33). These food-based recommendations incorporate advice from the DGA and use DRIs as nutrient intake goals. One alternative to the MyPyramid plan for meeting nutrient needs is the National Heart, Lung, and Blood Institute's Dietary Approaches to Stop Hypertension Eating Plan (32).

DIETARY GAPS

Many Americans do not consume the amount and types of foods necessary to meet recommended micronutrient intakes. Adherence to the DGA is low; only about 3% to 4% of Americans follow all of the DGA (34). As a result of low intakes of nutrient-rich foods and sedentary lifestyles, many Americans may be meeting or exceeding their energy requirements while falling short of vitamin and mineral recommendations. In assessing the diets of population groups, the proportion with intakes less than the EAR (not the RDA) are interpreted as estimates of the prevalence of inadequacy (24). The DGA identify calcium, potassium, magnesium, vitamin E, and fiber in adults and children, and vitamins A and C in adults only, as nutrients of concern (ie, nutrients for which the prevalence of inadequate intakes were high—in this case ≥40%—or for which low intakes were associated with public health problems) (35). Also identified as nutrients of concern were vitamin B-12 in older adults; vitamin D in older adults, people with dark skin, and people with inadequate exposure to sunlight; iron in adolescent females and women of childbearing age who may become pregnant; and folic acid in women of childbearing age and pregnant women (32).

An analysis of intake data from *What We Eat in America*, National Health and Nutrition Examination Survey 2001-2002 indicated potential for problems for vitamins A, E, and C and magnesium for most age/sex groups; vitamins B-6 for older adult females; zinc for all older adults and teenaged females; and phosphorus for preteen and teenaged females (36). In addition, the following nutrients may also be of concern because a low percentage of intakes were above AI levels (adequacy cannot be determined because the EARs needed for assessing adequacy have not been established for these nutrients): vitamin K, calcium, potassium, and dietary fiber (36). This analysis included intakes from food sources only.

According to national survey data, inadequate intakes from food sources are most prevalent for vitamin E and magnesium. Overt symptoms of vitamin E deficiency are uncommon in the United States (37). According to the IOM, actual vitamin E intakes may be higher than reported in national surveys for several reasons, including respondents underreport energy and fat intakes (source of vitamin E), inaccurately estimate amounts of fats and oils they add during food preparation and uncertainty about the types fats or oils consumed (37). Authors of a balance study suggested that the EAR for magnesium is set too high and that it should be lowered from 330 to 350 mg/day for men and 255 to 265 mg/day for women to 165 mg/day for healthy persons regardless of age or sex (38).

NUTRIENT SUPPLEMENTATION

Effect on Total Nutrient Intakes

Nutrient supplements can have a substantial impact on a person's total nutrient intake (39). Supplements have the potential to fill dietary gaps but, at the same time, may increase intakes above ULs. Thus, intake from supplements must be included along with intakes from conventional and fortified foods and beverages when assessing nutritional adequacies and excesses of individuals and population groups. With regard to supplements, The DGA state that:

> Supplements may be useful when they fill a specific identified nutrient gap that cannot or is not otherwise being met by the individual's intake of food. Nutrient supplements cannot replace a healthful diet. Individuals who are already consuming the recommended amount of a nutrient in food will not achieve any additional health benefit if they also take the nutrient as a

supplement. In fact, in some cases, supplements and fortified foods may cause intakes to exceed the safe levels of nutrients (32).

National survey data suggests that supplements may be taken by those who have healthful diets and lifestyles more often than those at a greater risk for vitamin and mineral inadequacies.

Filling Dietary Gaps. When taken regularly, MVMs can be an effective way to increase nutrient intakes to meet recommended levels of multiple nutrients. The extent to which a MVM can improve nutrient adequacy is impacted by the nutrient profile of the supplement taken. Of the nutrients previously identified as being low enough in diets to be of concern, MVM supplements have been shown to decrease the prevalence of nutrient inadequacy most notably for vitamin E, vitamin A, zinc, and vitamin B-6 (39). MVMs are less likely to substantially increase intakes of key nutrients such as calcium, magnesium, and potassium. Increasing consumption of foods rich in these nutrients will still be necessary to meet recommended amounts. In some cases such as with calcium, an additional supplement may be considered to help meet recommended intakes, particularly in at-risk groups (eg, older adults) where supplementation has been shown to have positive outcomes.

Based on 1994-1996 Continuing Survey of Food Intakes by Individuals data, when intake from supplements were added to food intakes of users, the percentage of older adults with inadequate intakes was reduced by at least three quarters for vitamin B-6, folate, vitamin C, and zinc in both men and women and vitamins A and E in men only (40). In addition, the prevalence of inadequate magnesium intakes was reduced from 71% to 41% in men aged ≥71 years and 64% to 29% in women (40). The prevalence rates for inadequacy in these women were also reduced from 18% to 6% for vitamin A and 93% to 17% for vitamin E. Most already met the EAR for iron and vitamin B-12 from food intakes, thus supplementation did not have a great influence on the proportion of subjects with adequate intakes. For calcium, the use of supplements increased the percentage with intakes above the AI from <3% to 14% in women aged ≥71 years and from 10% to 24% in men of the same age group when intakes of supplements were added to their intakes from food (40).

Exceeding ULs. There is potential for supplement users to exceed the ULs of some nutrients when they take high dose supplements or multiple products with the same ingredients, and even when MVMs are taken along with a diet rich in fortified foods. As daily intakes exceed the UL, risk of adverse health effects increase. In the Hawaii Los Angeles Multiethnic Cohort 1999-2001, the nutrients identified as those most likely to exceed the ULs were: iron, zinc, vitamin A, and niacin (39). The percentage of supplement users with intakes above the UL for folate was not estimated because intake from supplements only was not available. Based on 1994-1996 Continuing Survey of Food Intakes by Individuals data, the percentages of groups of older adult supplement users that exceeded the ULs ranged between 8% and 17% for iron, 4% and 15% for zinc, and 4% and 9% for vitamin A (40). Excess folate and niacin was not assessed. The percentages above UL levels for vitamin B-6, vitamin C, and calcium were <3%. In the 2002 Feeding Infants and Toddlers Study, intakes of toddlers between 12 and 24 months old using supplements exceeded the ULs for vitamin A, zinc, and folate more often than nonusers (41). The percentage of intakes exceeding the ULs for toddlers among nonusers compared to users were 15% and 97% for vitamin A, 38% and 68% for zinc, and <1% and 18% for folate, respectively (41).

Effect of Supplementation on Chronic Disease Prevention

Although MVM supplementation can be effective in helping meet recommended levels of some nutrients, evidence has not proven them to be effective in preventing chronic disease. A study published in 2009 from the Women's Health Initiative found no association between MVM supplementation and cancer or cardiovascular disease risk or total mortality in postmenopausal women (42). In 2006, a National Institutes of Health State-of-the-Science Panel reviewed evidence, including an evidence-based review of literature that was limited to randomized controlled studies, on the health benefits and risks of MVM supplements (defined as "any supplement containing three or more vitamins and minerals but no herbs, hormones, or drugs, with each component at a dose less than the Tolerable Upper Intake Level") (43). The panel concluded that evidence, at the time, was insufficient to determine whether or not taking MVM supplements was beneficial in preventing chronic disease in generally healthy people (43).

The evidence on supplemental calcium and vitamin D in relation to bone health has been favorable, particularly in older women. The National Insitutes of Health State-of-the-Science Panel on MVM supplements concluded that when used in combination, calcium and vitamin D supplements increase bone mineral density and decrease risk of hip and nonvertebral fracture in postmenopausal women (43). An evidence-based analysis of the literature on vitamin D and bone health outcomes found that vitamin D-3 (700 to 800 IU daily) with calcium (500 to 1,200 mg) resulted in small increases in bone mineral density and reduced fall risk in older adults and reduced risk of fractures in elderly women living in nursing homes (44).

NUTRIENT SUPPLEMENTS IN PRACTICE

When to Consider Supplementation

Nutrient supplements can be used to help meet a nutrient requirement or to treat a diagnosed deficiency disease. A person's micronutrient intake may be inadequate when they are restricting energy intake for weight loss/control, not consuming an adequate amount of food to meet energy requirements as a result of poor appetite or illness, eliminating one or more food groups from their diet on a regular basis, or consuming a diet low in nutrient-rich foods despite adequate or excessive energy intakes. Among the groups most vulnerable to inadequacy of one or more nutrients are older adults; pregnant women; people who are food insecure (ie, they are, "at times, uncertain of having, or unable to acquire, enough food for all household members because they had insufficient money and other resources for food") (45); alcohol-dependent individuals; strict vegetarians and vegans; and those with increased needs due to a health condition or the

chronic use of a medication that decreases nutrient absorption or increases metabolism or excretion.

Some government and professional organizations and expert workgroups provide recommendations for nutrient supplementation. ADA position papers that focus on particular segments of the population, nutrients, or conditions often include recommendations on nutrient supplementation. The following are examples of these nutrient supplement recommendations.

- **Infants and children, including adolescents** The AAP recommends the following groups of healthy infants and children receive 400 IU daily of supplemental vitamin D: all infants who are exclusively or partly breastfed (beginning the first few days of life and continued unless infant is weaned to at least 1 qt/day vitamin D–fortified formula or, if older than 12 months, whole milk or low-fat milk when appropriate); all non-breastfed infants and older children who consume less than 1qt/day vitamin D–fortified formula or milk; and adolescents with dietary intakes <400 IU/day (30). Children at an increased risk for vitamin D deficiency, such as those with fat malabsorption and those taking seizure medications, may need higher amounts to achieve normal vitamin D status as determined by lab results (30).
- **Women of childbearing age who may become pregnant** The DGA and IOM recommend that women who can become pregnant consume 400 μg/day of folic acid from fortified foods and/or supplements daily, in addition to folate obtained from eating a varied diet, to reduce the risk of neural tube defects (eg, spina bifida and anencephaly) (35,46).
- **Pregnant women** The DGA recommend pregnant women consume 600 μg/day of folic acid from fortified foods or supplements in addition to dietary folate (32). The RDA of dietary folate equivalents for pregnant women is 600 μg/day (46). The ADA position paper, "Nutrition and Lifestyle for a Healthy Pregnancy Outcome" (47), recommends MVM supplementation for pregnant women who have iron deficiency anemia or poor-quality diets, consume no or small amounts of animal sources, are carrying two or more fetuses and smoke or abuse alcohol or drugs. The ADA position paper also recommends supplementation with 27 mg iron daily (60 mg daily if she has anemia) and with vitamin B-12 in some vegans or lacto-ovo vegetarians (47).
- **Older adults** The DGA and IOM recommend that people over age 50 get 2.4 μg/day vitamin B-12 mainly from the crystalline form found in fortified foods and supplements (32,46). Age is associated with conditions like atrophic gastritis that may reduce a person's ability to digest food-bound vitamin B-12 (46). The DGA recommend older adults consume extra vitamin D from vitamin D–fortified foods and/or supplements (32). This is because older adults are at risk for low serum 25(OH)D concentrations because they have a decreased ability of the skin to synthesize vitamin D from sunlight (ultraviolet B radiation) compared to younger adults (48) and some may have limited exposure to sunlight. The Modified MyPyramid for Older Adults developed by researchers at Tufts University, includes a flag on top of the pyramid to alert people older than age 70 years of the potential need to supplement the diet with vitamins B-12 and D and calcium (49). Calcium was included in the flag because the diets of many older adults are below recommended levels.
- **People at risk for suboptimal vitamin D status** The DGA recommend that in addition to older adults, people with dark skin (because they have a decreased ability to synthesize vitamin D from sunlight), and those exposed to insufficient sunlight, consume extra vitamin D from vitamin D–fortified foods and/or supplements (35).

ADA EAL

This portion of the position paper includes the results of a systematic review of literature conducted using ADA's Evidence Analysis Process and information from ADA's EAL. In this process, an expert work group identified dietetic practice related questions, performed a systematic review of the literature and made and rated a conclusion statement for each question. The workgroup used ADA's process to answer a total of seven questions related specifically to the supplementation of vitamins B-12 and D in older adults.

To identify and select articles for review, the National Library of Medicine's PubMed database was searched using the term older adults and the name of the respective vitamin (eg, vitamin D or cholecalciferol and vitamin B-12 or cobalamin or cyanocobalamin). All study designs, except case studies, were included in the search. Articles published from January 2006 to January 2008 with sample size ≥20 individuals per study group and with less than a 20% dropout rate were searched. Studies were also identified by screening the reference lists of the selected papers. Identified papers were then excluded if they did not provide an answer directly related to the question. In addition, for questions related to vitamin D, a decision was made after the initial search to exclude papers published before January 2006 due to the inclusion of a 2007 Agency for Healthcare Research and Quality evidence-based review that incorporated research before this date.

The detailed search plan and results and information on the process and how the conclusions of the Fortification and Supplements Evidence Analysis Project were reached are available at the EAL Web site (50). The conclusion statements and grade for the strength of the evidence for each question are provided below.

In addition to the Fortification and Supplements Evidence Analysis project, several other ADA evidence analysis projects have included questions related to the use of vitamins and minerals as they pertain to dietetics practice. To date, most questions on the EAL on micronutrient supplementation relate to cardiovascular disease and oncology.

Vitamin B-12

What is the evidence regarding the effect of oral vitamin B-12 supplementation and/or fortification on serum cobalamin levels in deficient older adults?

Conclusion statement Thirteen studies (eight randomized control trials [RTCs], one non-RTC, three cohort

studies, one cross-sectional study) found a dose–response effect in the administration of oral cobalamin to cobalamin-deficient older adults. Two of these studies used multivitamin mineral supplements containing 6 μg vitamin B-12 and the remaining studies used oral cobalamin ranging from 2.5 μg to 2,000 μg per day. Research endpoints were measured using serum cobalamin or serum methylmalonic acid levels. Four studies compared oral B-12 supplementation to intramuscular injection and concluded that oral supplementation was as effective as intramuscular supplementation. All of the studies used doses of vitamin B-12 greater than the current RDA of 2.4 μg per day for older adults. Further research is needed to define serum cobalamin deficiency and to determine appropriate levels of oral cobalamin supplementation in deficient older adults. **Grade II=Fair.**

Are serum cobalamin concentrations associated with cognitive function in older adults?

Conclusion statement Research is inconclusive regarding specific serum cobalamin levels associated with cognitive function in older adults. Five studies (one RCT, one non-RCT, two cross-sectional studies, and one prospective cohort study) found an association between low serum cobalamin levels and impaired cognitive function in older adults. Four studies (one cross-sectional, three RCTs) found no significant difference in cognitive function in individuals with normal and deficient cobalamin levels. One additional study (an RCT) found a decline in cognitive function with supplementation in cobalamin deficient adults compared to placebo and another study (cross-sectional) found deteriorating cognitive function in cobalamin- and folate-deficient individuals.

Current research is limited by lack of a standardized definition of vitamin B-12 deficiency and lack of standardized measures of cognitive function. Further research is needed to establish the role of vitamin B-12 in cognitive function in older adults. **Grade III=Limited.**

Vitamin D

What is the evidence regarding the effect of supplemental vitamin D on bone density in postmenopausal women and older adult men?

Conclusion statement One meta-analysis (a systematic review of 19 studies), five RCTs, and two cross-sectional studies found an association between supplemental vitamin D and bone mineral density in postmenopausal women and older adult men. Vitamin D dosage ranged from 400 IU to 1,400 IU (10 μg to 35 μg) per day; however, it is difficult to determine the optimal dosage and the effect of vitamin D alone, since varying combinations of nutrients were used including calcium and vitamin K. One additional RCT with a supplement containing 200 IU (5 μg) vitamin D and other nutrients found an improvement in bone turnover markers, but no effect in bone mineral density. Further research is needed to determine the independent association between supplemental vitamin D and bone mineral density in postmenopausal women and older adult men. **Grade II=Fair.**

What is the evidence regarding the effect of supplemental vitamin D on fractures in postmenopausal women and older adult men?

Conclusion statement One meta-analysis/systematic review, combining the results of 13 RCTs, suggests that supplementation with vitamin D-3 (400 IU to 800 IU) plus calcium (500 mg to 1,200 mg) may be beneficial in reducing the incidence of fractures in institutionalized older adults. The reduction of fractures might be accounted for by higher mean serum levels of 25(OH)D (at least 74 nmol/L), due to good volunteer compliance. One RCT concluded that supplementation with 100,000 IU vitamin D-2 every 4 months does not significantly reduce fractures in institutionalized older adults. Further research is needed to determine the role of vitamin D-3 and D-2 supplementation alone in reducing the incidence of fractures. **Grade II=Fair.**

What is the evidence regarding the effect of supplemental vitamin D on falls in postmenopausal women and older adult men?

Conclusion statement One meta-analysis/systematic review, one RCT, and one prospective cohort study found that evidence is inconsistent regarding the effect of supplemental vitamin D-2 or D-3 on the reduction of falls in older adult men and women. Further research is needed to determine the role of vitamin D-2 or D-3 alone in preventing falls in older adults. **Grade III=Limited.**

Are specific circulating concentrations of 25(OH)D associated with bone health outcomes in postmenopausal women and older adult men?

Conclusion statement Two RCTs and one meta-analysis (a systematic review of 42 papers) found that evidence is inconclusive regarding the association of specific circulating concentrations of 25(OH)D and bone health outcomes in postmenopausal women and older adult men. In those studies reporting a positive association in the meta-analysis, specific 25(OH)D concentrations ranging from 40 to 80 nmol/L were shown to have declines in bone health outcomes (fractures, falls, and bone loss). Further research is needed to determine the association of specific circulating concentrations of 25(OH)D with bone health outcomes. **Grade III=Limited.**

What is the effect of vitamin D supplementation on circulating 25(OH)D in postmenopausal women and older adult men?

Conclusion statement Two RCTs and one meta-analysis (systematic review of 44 RCTs) found a direct effect of oral vitamin D-3 supplementation on circulating levels of 25(OH)D in postmenopausal women and older adult men. In studies reporting a treatment effect, specific doses ranging from 5 μg to 50 μg (200 to 2,000 IU) vitamin D-3 were utilized. Meta-regression results suggested that 100 IU (2.5 μg) vitamin D-3 will increase the serum 25(OH)D concentrations by 1 to 2 nmol/L suggesting doses of 400 to 800 IU (10 to 20 μg) daily may be inadequate to prevent vitamin D deficiency in at-risk individuals. It is difficult to determine adequate intake since there is a lack of agreement regarding optimal levels of serum 25(OH)D. Additional research is needed to determine the vitamin D dosage necessary to reach optimal serum 25(OH)D levels in postmenopausal women and older adult men. **Grade II-Fair.**

Assessing Need for Nutrient Supplements

To support an optimal nutritional status, nutrient consumption should ad-

equately meet requirements including any metabolic demands such as those that may be a result of genetics, age, stress, and infection and disease states. The strategies of nutrition assessment, the first of the four steps of the Nutrition Care Process, enable a dietetics practitioner to gauge the need for nutrient supplementation (51,52). The assessment process should include a comprehensive evaluation of medical, social, and food and nutrition-related history, anthropometric measurements, biochemical data, medical tests and procedures and nutrition-focused physical examination (53).

Issues to Consider

Total Nutrient Intakes. Intake assessments must include all nutrient sources including natural and fortified foods and dietary supplements; both nutrient adequacy and excess could be underestimated if only conventional food sources are considered. One way to do this is to include open-ended questions about the consumption of nutrient supplements when collecting nutrition data. Questions pertaining to dietary supplement use may include the name and manufacturer of the product, the frequency, the dose, and the duration of use (54). Clients using multiple supplements can be asked to bring in the containers of supplements used, particularly if products with multiple ingredients are used.

Food and nutrition-related histories, food records, 24-hour recalls, and food frequency questionnaires are methods often used to assess dietary intakes. New methods to analyze total nutrient intakes are being used with varying degrees of success. One method, a Web-based automated 24-hour recall, is available from the National Cancer Institute (55). Food frequency questionnaires that include information on nutrient content of fortified foods and nutrient supplements, such as the validated self-administered Short Calcium Questionnaire, are available to quickly estimate calcium intake (56).

Laboratory Analyses. Laboratory analyses can be performed for vitamins A, C, D, E, K, thiamin, riboflavin, niacin, vitamins B-6 and B-12, and folic acid and the minerals iron, copper, iodine, zinc, manganese, and selenium (57). Additional laboratory tests can be helpful in assessing nutrient status for some nutrients. For example, serum ferritin is a sensitive indicator of body iron status except in situations of inflammation, infections, or neoplastic disorders (53). Serum iron and transferrin saturation are also useful in evaluating iron status. In the practical setting, however, laboratory analyses of most vitamins and minerals are not generally available. Cost and lack of cut-off points for defining suboptimal nutritional status for some nutrients limit their use in practice. Nutrition-focused physical findings can also be useful when assessing nutritional status for some nutrients including vitamins A, C, D, riboflavin, niacin, and vitamins B-6 and B-12 (57).

Genetics/Genomics. The evolving science of nutrigenomics examines the interaction between specific genes and nutrients (58). This emerging science may provide insight into how nutrition influences metabolic pathways and homeostatic control, and how dietary intervention strategies can be used to promote health and prevent disease in individuals with different genotypes (58). Micronutrients such as calcium, zinc, selenium, folate, and vitamins C and E are known to modify disease-related processes such as carcinogen metabolism, hormonal balance, cell signaling and cycle control, apoptosis, and angiogenesis (59). For example, the reduced incidence of a variety of cancer types linked to supplementation with selenium is influenced by genetic variability that governs individual responses (59). Methylation of DNA, influenced by intake of micronutrients such as selenium; vitamin A, B-6, and B-12; choline; zinc; methionine; and others, can influence epigenetic processes which affect gene expression or activation without changing DNA sequence (59). This has been looked at in relation to the role of maternal diet on the susceptibility of the offspring to diseases and nutrition-related conditions such as diabetes and cancer (59). Identification of single nucleotide polymorphisms in individuals may enhance our understanding of why someone with a genetic variant could react negatively or favorably to supplementation. This is particularly relevant to the potential benefits of supplemental folate with respect to homocysteine metabolism and reduction of cardiovascular disease risk where a gene variant decreases the activity of methylenetetrahydrofolate reductase, a folate-metabolizing enzyme (60). As a result, homocysteine accumulates unless folate supplements are prescribed (53). In the future, use of DNA microarrays (61) to identify individual genetic variation may be among the assessment tools used to advise clients of their nutrient and supplement needs and to measure the efficacy of nutrition prescriptions (61). Ultimately, by taking into account the known genetic variability in patients and clients, nutrient supplementation can be better tailored to the individual with the goal of disease prevention.

Contraindications. Dietetics practitioners must be aware of possible situations in which individuals may need to temporarily or permanently limit or avoid specific nutrient supplements due to the potential for adverse effects. For example, healthy postmenopausal women and adult men generally should not take iron supplements. The prevalence of inadequate iron intakes among older adults is low (40). Thus, concern of excess iron intakes may be greater than inadequate intakes. Avoiding iron supplementation is particularly important for individuals homozygous for hemochromatosis and those with blood disorders requiring frequent blood transfusions (62,63). To be cautious, smokers should avoid supplementation with beta carotene because increased risk of lung cancer and increased mortality have been associated with high-dose beta carotene supplements in this group (64). Postmenopausal women who take supplements containing vitamin A should consider a product that contains a majority of the vitamin A from beta carotene sources rather than retinol. Intakes of more than 1,500 μg/day vitamin A from retinol, but not beta carotene, compared to intakes of 500 μg/day, have been associated with increased risk of hip fracture and reduced bone mineral density in postmenopausal women (65). In addition, some dietary supplements are contraindicated during surgery. For example, it has been recommended that

because vitamin E acts as a blood thinner, supplements of the vitamin should be avoided at least 1 week before surgery (53).

Nutrient Excess. Certain vitamins have been associated with adverse effects at high doses. For example, excess folic acid may mask or exacerbate symptoms of a vitamin B-12 deficiency (66). Excessively high supplemental intakes of vitamin B-6 have been reported to result in sensory neuropathy (46). Gastrointestinal disturbances, kidney stones, and excess iron absorption, particularly for individuals with excessive iron absorption due to hereditary hemochromatosis, is cited as the possible adverse effects of excessive consumption of vitamin C (37).

Nutrient Interactions. Dietetics practitioners should also be aware of and document the potential nutrient/nutrient and drug/nutrient interactions that can occur with the chronic use of nutrient supplements (67). An imbalance of nutrients, such that the amount of one nutrient interferes or alters absorption and/or utilization of another nutrient, can result from the consumption of high-dose nutrient supplements. For example, high-dose iron supplements can decrease zinc absorption and high amounts of zinc can inhibit copper absorption (68). The absorption of supplemental magnesium in the form of magnesium salts is inhibited by iron supplements, whereas the absorption of both heme- and non-iron is inhibited by calcium supplements (62); thus, individual supplements of minerals, if indicated, should be taken separately.

Drugs can increase the requirement for certain nutrients and compromise nutritional status. For example, anticonvulsant medications can increase the need for folate (69). Corticosteroids can deplete calcium (48) and impair vitamin D metabolism (70). Certain diuretics, antibiotics, and antineoplastic medication can cause a magnesium deficiency (71). Chronic alcohol consumption can increase the requirement for B vitamins and magnesium due to decreased absorption, increased diuresis, and increased metabolism of these nutrients (69,71-73). Multiple medications managing multiple diseases (polypharmacy), particularly among older adults, can increase the likelihood of drug/nutrient interactions and influence the need for certain nutrients.

Nutrient supplements can influence the dosage and/or bioactivity of medications. For example, vitamin K supplementation can decrease the effectiveness of anticoagulant medications like warfarin. Supplements containing vitamin K should be avoided or used with caution and under the medical care of a physician by those taking such medications as a consistent intake of the vitamin is critical. Vitamin E, which can inhibit platelet aggregation and antagonize the actions of vitamin K, may also interact with anticoagulant and antiplatelet medications (74). High-dose vitamin E supplements may increase the risk of bleeding in individuals taking these medications (74). Resources that provide information on precautions, contraindications, and potential interactions with drugs, food or other supplements include the Office of Dietary Supplements' fact sheets (75) and the *PDR for Nutritional Supplements* (76). Additional sources are provided in the Figure.

Supplement Forms and Dosages. Certain forms of nutrients are more likely than others to contribute to nutrient adequacy based on their molecular structure and chemical formula. For example, folic acid from supplements and fortified foods is more bioavailable than folate from foods due to the ease of absorption of the unconjugated form (46). Other issues of supplement selection, such as the chemical form, can affect both adverse effects and efficacy. For example, the pharmacological use of niacin (nicotinic acid), may be effective as a lipid-lowering agent, but may also cause side effects such as flushing and itching (77). Strategies such as slowly increasing doses and taking aspirin may help prevent or minimize the discomforts of niacin therapy (78). The effects of the two forms of supplemental vitamin D (D-2 or ergocalciferol made from yeast and D-3 or cholecalciferol from animal sources) on serum levels of 25(OH)D have been compared. Some studies report a significantly greater effect of vitamin D-3 on increasing the levels of serum 25(OH)D (44,79) while a more recent study found that the two forms of the vitamin were equally effective (80). These discrepancies in the literature speak to the pressing need for updated guidelines for the treatment of vitamin D insufficiency in healthy adults (81).

The effectiveness of mineral supplements is affected by the amount of the elemental mineral present in the mineral salt. Due to the bulk of calcium salt, it is impossible for calcium at recommended amounts to be included in a reasonably sized MVM supplement (82). Calcium carbonate has the highest concentration of calcium among calcium salts but requires an acid medium for optimal absorption. Thus it is recommended that it be consumed with meals (83). Calcium citrate can be taken with or without foods and can be used by those with achlorhydria (84). Calcium lactate and gluconate are less useful due to the minimal content of calcium in these supplements. Maximum absorption is obtained with doses $\leq$500 mg, so splitting a 1,000 mg dose into two doses is advisable (85). Magnesium chloride and magnesium lactate are more bioavailable than magnesium oxide (71). In addition, enteric coating on supplements can block the absorption and bioavailability of magnesium supplements (71).

Reporting Adverse Effects

Dietetics practitioners are urged to counsel clients to report adverse reactions to nutrient supplements to the manufacturer and to the FDA. Health care professionals are also encouraged to report adverse effects experienced by their clients from the use of dietary supplements using the FDA's MedWatch program. The Health Insurance Portability and Accountability Act Privacy Rule permits covered entities to "report adverse events and other information related to the quality, effectiveness, and safety of FDA-regulated products both to the manufacturers and directly to the FDA" (86). Reports can be made by telephone by calling 800-FDA-1088 or online at www.fda.gov/Safety/MedWatch/HowToReport/ucm085568.htm (87).

PROFESSIONAL RESOURCES

The Office of Dietary Supplements at the National Institutes of Health, which was created in part to promote

research aimed at determining the health benefits and risks of dietary supplements, provides several tools dietetics practitioners can use to increase their knowledge of dietary supplements. These include a 1-week practicum on dietary supplement issues for nutrition and health-related faculty and graduate students (88); the International Bibliographic Information on Dietary Supplements database, which contains citations and abstracts from the scientific literature on dietary supplements (89); and expert-reviewed fact sheets on dietary supplement ingredients (75). These and other resources such as those listed in the Figure can be used by dietetics practitioners to stay informed on issues related to dietary supplements.

ROLES AND RESPONSIBILITIES OF DIETETICS PRACTITIONERS

Given the prevalent use of nutrient supplements by the public, dietetics practitioners need to keep up-to-date on the safety and efficacy of these products to assist consumers in the safe and appropriate use of supplements. The roles and responsibilities of dietetics practitioners include:

- assessing nutritional status of clients to determine likelihood of inadequate or excessive intake of vitamins and minerals;
- evaluating the potential benefit or harm of nutrient supplementation given a client's nutritional and health status;
- evaluating the safety of a nutrient supplement given the form, dose, its potential for interaction with food, other dietary supplements and over-the-counter and prescribed medications;
- educating clients as to the potential benefit of receiving nutrients through conventional and fortified foods;
- recommending nutrient supplementation when food intake is inadequate;
- evaluating research regarding nutrient supplementation; and
- being aware of regulatory, legal, and ethical issues of recommending and selling of nutrient supplements.

These are clearly challenging yet critical roles and responsibilities for dietetics practitioners. Continuing education and inclusion of dietary supplements in didactic curricula are essential to ensuring dietetics practitioners have the skills necessary to perform these functions.

CONCLUSIONS

Consumption of a wide variety of nutritious foods is the best way to maintain health and prevent chronic disease. The dietary intakes of many Americans do not meet recommended nutrient intake levels. It is among the roles and responsibilities of dietetics practitioners to help educate the public on healthful dietary patterns and on the safe and appropriate selection and use of nutrient supplements to meet their nutrient needs and optimize health. To this end, dietetics practitioners must keep abreast of research findings on potential benefits and safety of nutrient supplements and on the regulations that govern these products.

To obtain references used for the evidence analysis sections of this position, go to www.eatright.org/cps/rde/xchg/ada/hs.xsl/advocacy_15986_ENU_HTML.htm.

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