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INSIDE

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Russell H. Greenfield, MD (executive editor) and Paula Cousins (senior managing editor) have no financial relationships with companies having ties to the material presented in this continuing education program.

Vitamin D and Musculoskeletal Health in the Elderly: Have We Seen the Light?

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In 1969, a band called the Fifth Dimension popularized the refrain "Let the sun shine in," in a hit song from the Broadway musical *Hair*, though it is doubtful they were advocating for the increased cutaneous manufacture and dietary intake of vitamin D. Over the past four decades, however, numerous clinical studies have uncovered the importance of this "sunshine vitamin" to skeletal, neuromuscular, and overall general medical health. Despite this knowledge, there continues to be a high incidence of vitamin D insufficiency in the United States and worldwide, which affects more than 1 billion persons.[1] Though virtually all population subsets have vitamin D deficiency, certain groups, particularly elderly home-bound or long-term care residents, are disproportionately affected.[2,3]

The lack of vitamin D has significant ramifications for both diminished bone health and overall general medical health due to increased vulnerability to osteoporosis, osteomalacia, falls, fracture, and tooth loss. Given that hypovitaminosis D is a treatable condition, heightened awareness is necessary among primary care physicians to ensure adequate vitamin D nutrition to vulnerable populations. Part 1 of this series will focus on the relationship between vitamin D and musculoskeletal health; part 2 will focus on its relationship to periodontal disease and loss of dentition, areas of importance to quality of life and health in geriatric patients.

Sources of Vitamin D

Two forms of vitamin D are vitamin D2 (ergocalciferol), derived from irradiation of the yeast and plant sterol ergosterol, and vitamin

VOLUME 12 • NUMBER 4 • APRIL 2009 • PAGES 37-48

D3 (cholecalciferol) found in fatty fish and manufactured in the skin. The vitamin D from food and supplements is primarily in the form of D3 (D). Few foods aside from oily fish and egg yolks naturally contain vitamin D. For this reason, in the United States, dairy products such as milk, certain cereals, and juices are fortified with vitamin D.

Exposure of skin to sunlight can also generate vitamin D; however, several factors influence vitamin D skin synthesis *(see Table 1, page 39)*.[4-8] In general, exposure of the arms and legs to sunlight for an average of 5-30 minutes from 10 am to 3 pm twice a week is adequate.[4,6,9] Although darker skinned individuals genetically have lower bone turnover and 9-11% greater bone mineral density than whites, they are at increased risk for osteoporosis and fractures because melanin serves as an effective sunscreen, thus putting them at risk for vitamin D, as well as calcium, insufficiency.[10]

Photobiology and Metabolism of Vitamin D

The initial step in the photochemical production of vitamin D occurs when solar ultraviolet B radiation (UVB; 290-315 nm wavelength) penetrates the skin to convert the precursor 7-dehydrocholesterol in the epidermis to previtamin D3, which is then thermodynamically converted to vitamin D3. This UVB-mediated cutaneous synthesis does not cause vitamin D intoxication because any excess vitamin D or previtamin D is converted to biologically inert photoproducts. Additionally, epidermal cells can produce the active $1,25(OH)_2D$ locally, which can regulate cellular differentiation and melanin production, and provides negative feedback to modulate further vitamin D cutaneous production.

Summary Points

- Given its broad endocrine and paracrine functions, vitamin D plays an important role in overall general health, particularly musculoskeletal health. Vitamin D requirements for individual patients depend upon their medications and medical conditions.
- Geriatric patients represent an at-risk population for hypovitaminosis D and benefit from an assessment of their serum 25(OH)D levels, the depot form of vitamin D, during periodic physical evaluations.
- Clinical studies have established that serum levels maintained in the 30-40 ng/mL (75-100 nmol/L) range with an intake of 800 IU vitamin D or greater in conjunction with sensible sun exposure and at least 1,200 mg of calcium improve muscle strength and balance, thereby reducing the risk of falls and fragility fractures that cause disability.

Dietary and cutaneously derived vitamin D, complexed to chylomicrons, is absorbed and transported via lymphatics to the venous system or to adipose depots. In the circulation, vitamin D3 undergoes enzymatic modification (by hepatic D-25 hydroxylase) to 25(OH)D, the major circulating form of vitamin D. This inactive form is then converted in the kidneys (via the 25-hydroxyvitamin D-1 alpha hydroxylase enzyme) to the biologically active form, 1,25 dihydroxycholecalciferol [$1,25(OH)_2D$]. This rate-limiting step is tightly controlled by a variety of factors including serum parathyroid hormone (PTH) and phosphorus.[6]

The ratio of the total serum concentrations of the two major vitamin D metabolites, 25(OH)D and $1,25(OH)_2D$, is about 1,000:1. The 25(OH) vitamin D is used clinically to determine vitamin D status. Its long half-life of two weeks makes it suitable as a biomarker of vitamin D reserves.[9] Serum $1,25(OH)_2D$ values do not correlate with clinical disease status; therefore, information on serum $1,25(OH)_2D$ concentration is not useful for clinical diagnosis and treatment.[6]

Vitamin D and Calcium Homeostasis

The active vitamin D metabolite, $1,25(OH)_2D$, is one of the primary biologic regulators of calcium homeostasis and is more technically a steroid hormone. It is

Alternative Medicine Alert, ISSN 1096-942X, is published monthly by AHC Media LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

ASSOCIATE PUBLISHER: Coles McKagen
DIRECTOR OF MARKETING: Schandale Kornegay
SENIOR MANAGING EDITOR: Paula Cousins
GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Alternative Medicine Alert***, P.O. Box 740059, Atlanta, GA 30374.

Back Issues: $58 per issue. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Table 1

Physiological and physical factors affecting vitamin D synthesis in the skin[5,6]

Factor	Explanation
Season	Summer generates higher cutaneous vitamin D synthesis than winter
Geographic latitude	Areas above 37° N latitude and below 37° S latitude have decreased sunlight exposure during winter months[7]
Skin pigmentation	Increased melanin in darker skin reduces vitamin D skin synthesis[8]
Sunscreen use	SPF 8 decreases vitamin D skin synthesis by 93% SPF 15 decreases vitamin D synthesis by 95%[9]
Aging	7-dehydrocholesterol precursor levels decrease up to 75% by age 70[4]
Inadequate sun exposure	Chronic illness; institutionalization; clothing cover

believed to function in a similar fashion as other steroid hormones by binding with the vitamin D receptor (VDR), resulting in its biological effects on the kidney (down-regulates its own production), small intestine (increases the efficiency of calcium absorption), parathyroid glands (modulates PTH release), and on the bony skeleton (increases the mineral content) to regulate calcium and phosphorus blood levels.

Classification and Causes of Vitamin D Deficits in Geriatric Patients

The prevalence of vitamin D deficiency, 25(OH)D levels < 20 ng/mL or 50 nmol/L, is 41% in outpatients aged 49-83 years and up to 57% in hospitalized patients.[11,12] Certain medical conditions can cause or exacerbate vitamin D deficiency in the elderly *(see Table 2, page 40)*.[13-17]

Patients with osteoporosis are vulnerable to vitamin D inadequacy. As a matter of fact, 52% of postmenopausal women receiving osteoporosis medications have vitamin D insufficiency (levels < 30 ng/mL or 75 nmol/L) and, therefore, do not obtain the maximal benefit from their medications.[18] Patients with severe vitamin D deficiency, 25(OH)D levels < 10 ng/mL (25 nmol/L), have concomitant osteomalacia (defective mineralization of the skeletal osteoid matrix) and this condition causes generalized musculoskeletal pain, which may be misdiagnosed as fibromyalgia. Evaluation of the 25-hydroxyvitamin D status of such patients can provide a basis for treatment.

Degrees of immobility are important factors that affect skeletal, as well as general, health in geriatric (and other) populations. Sorva et al demonstrated that supplementation for very low levels of vitamin D (< 12 ng/mL or 15 nmol/L) slightly improved PTH levels but neither the increased vitamin D levels or the decreased PTH levels affected serum calcium levels or carboxyterminal crosslinked telopeptide of type I collagen levels (marker of bone resorption) in immobilized geriatric patients. Such observations suggest that interventions aimed at increasing physical mobility may augment the effects of vitamin D supplementation on skeletal health in addition to the other medical benefits of increased mobility for this population.[19]

Assessment of Vitamin D Status

When vitamin D levels are inadequate, calcium and phosphorus homeostasis is impaired. A panel of experts has determined that the optimal range of circulating 25(OH)D concentrations for optimal skeletal health: 1) reduces serum PTH levels to a minimum maintained level (approximately 20 pg/mL), and 2) increases intestinal calcium absorption to its maximal level (approximately 30-40% of dietary intake). This range of 25(OH)D blood levels is 30-40 ng/mL (75-100 nmol/L).[20]

Additionally, Lappe et al, in a 4-year prospective, population-based, double-blind, placebo-controlled trial of 1,180 white postmenopausal women (age > 55 years), found a decreased (nonskin) all-cancer (breast, colon, lung, uterus, hematopoetic) risk with improvement in vitamin D status to > 80 nmol/L.[21]

Candidates for Vitamin D 25(OH) Screening

Screening measurements of vitamin D 25(OH) levels are advised for all patients who are homebound or institutionalized, as well as patients who have known or are evaluated for osteoporosis. Patients with known impaired absorption and those with a medical risk factor listed in Table 2 are candidates for screening as well. Thus, it could be argued that all elderly patients, particularly elderly female patients, should be screened.

Consequences of Vitamin D Deficiency

Vitamin D deficits in adults diminish the efficiency of intestinal calcium absorption, which causes ionized calcium to drop, triggering PTH release. The secondary hyperparathyroidism stimulates osteoblast-mediated osteoclast activity, resulting in increased bony resorption with concomitant diminished bone mineral density (osteoporosis) and stability of the osteoid matrix

(osteomalacia) with increased risk for fragility fractures and diffuse musculoskeletal pain and dysfunction.[6]

Dietary Epidemiologic Data for U.S. Geriatric Population

According to NHANES III data, less than 10% of older adults (51-70 years of age) and 2% of the elderly (older than age 70) population met vitamin D requirements from dietary (food plus supplement) sources alone. Unfortunately, a follow-up study of the serum 25(OH)D status of the U.S. population from 2000 to 2004 demonstrated decreased levels of 5-9 nmol/L in comparison to NHANES III, particularly in a subgroup of white non-Hispanic males, despite adjustment for changes in assay measurements. This suggests that older men and women remain at risk for osteoporosis, osteomalacia, and significant disability from fragility fractures (osteoporotic or low-trauma fractures typically involving the distal radius, hip, and vertebral bodies).[22]

Fragility Fractures and Vitamin D

Approximately 30 million adults in the United States have osteoporosis of the hip. Hip fractures are the most serious and expensive of the fragility fractures and the risk increases exponentially with age. A Cochrane Review reported that 50% of osteoporotic fractures are nonvertebral and falls are the primary reason for these fractures.[23] Thirty percent of persons older than age 65 and 50% of persons older than age 80 fall each year. Such falls cause injuries that result in disability, loss of independence, and subsequent admission to a nursing home.[24-26]

Randomized trials[27] and population studies of elderly persons all found a significantly decreased incidence of hip fracture over several years of follow-up, provided serum hydroxyvitamin D levels were approximately 70 nmol/L (30 ng/mL) or greater.[28-30] Interestingly, Gerdhem et al also found a correlation of levels of 25-hydroxyvitamin D ≤ 50 nmol/L (20 ng/mL) with significantly decreased gait speed, Romberg balance test, and thigh muscle strength, all of which may have contributed to the two-fold increase in risk of fracture compared to women with 25(OH) vitamin D levels of 75 nmol/L (30 ng/mL) or greater. The RECORD trial showed no antifracture efficacy for patients receiving 800 IU of vitamin D daily; however, the mean 25(OH) vitamin D levels increased from 15.2 to 24.8 ng/mL, which is below the threshold levels that provide antifracture efficacy.[31]

Neuromuscular Benefits from Vitamin D Supplementation

There is support from clinical studies that vitamin D insufficiency contributes to age-related muscle weakness with decreased physical performance[32] and falls.[33] Vitamin D appears to stimulate muscle cell growth through the binding of the active 1,25 dihydroxyvitamin D metabolite to a specific vitamin D nuclear receptor in muscle tissue. Sorensen et al noted an increased number and size of type II (fast twitch) muscle fibers of elderly women after only three months of therapy.[34,35]

Another study provided additional support for the beneficial effect of vitamin D supplementation on muscle function. Pfeifer et al conducted a 20-month double-blind controlled trial of 242 ambulatory, healthy men and women older than age 70 treated with calcium (1,000 mg) alone or in combination with vitamin D (800 IU) and found a significant decrease in falls for the calcium plus vitamin D group [mean 25(OH)D levels after treatment, 84 nmol/L or 33.5 ng/mL]. Additionally, functional kinesthetic improvements,

Table 2

Medical conditions contributing to vitamin D deficiency

Condition	Mechanism
Obesity	Sequestration of 25(OH)D in adipose decreases bioavailability[15]
Hyperthyroidism	Decreases production of active $1,25(OH)_2D$[16]
Fat malabsorption syndromes: Crohn's disease, celiac sprue, chronic pancreatitis;	Diminish absorption of vitamin D[17]
chronic liver disease	Diminishes hepatic 25 hydroxylation
Medication use: glucocorticoids;	Decrease VDRs[18]
bile acid sequestrants;	Decrease vitamin D absorption
anticonvulsants (dilantin, tegretol, phenobarbital)	Interfere with hepatic 25 hydroxylation[19]
Renal insufficiency	Diminishes production of active $1,25(OH)_2D$
Inflammatory diseases (rheumatoid arthritis)	TNF-α decreases renal production of active $1,25(OH)_2D$[18]

such as an 8% increase in quadriceps strength and an 11% decrease in the time to perform the up and go test (TUG), were seen only in the calcium plus vitamin D group.[36]

Considerations for Over-the-Counter Vitamin D Supplements

The selection of supplements with the USP (United States Pharmacopoeia) Dietary Supplement Verification Program certification logo insures that the product contains the amount of vitamin D specified on the label and is free of contaminating substances such as lead.[37] Since neither the FDA nor other federal or state authorities routinely test over-the-counter vitamin D or calcium supplements for quality issues, it is important to identify and use products that have been independently tested by laboratories such as ConsumerLab.com.[38] ConsumerLab tests products for: content (verification of the amount of calcium and vitamin D indicated on the label); purity (the product is not contaminated with lead or other substances that may pose health problems); and absorbability (the product is formulated for efficient absorption from the gut).

Dosages for Geriatric Patients: Vitamin D

It is most cost-effective to use vitamin D3 (cholecalciferol) or vitamin D2 (ergocalciferol) supplements for patients adherent to vegetarian or vegan diets. Some studies have indicated diminished potency (less than one-third that of D3) and duration of action for D2 supplements,[39,40] whereas other studies have shown relative equipotency.[41]

Vitamin D3 is available in 400, 1,000, 5,000, and 50,000 IU capsules and D2 is available as 400 IU and 50,000 IU capsules. Clinical studies showed a threshold effect for vitamin D: A minimal dose of vitamin D of 700-800 IU/d alone[42,43] or in combination with at least 500 mg/d of calcium was effective in significantly reducing fracture risk,[44] whereas a dose of 400 IU/d was not effective at preventing falls in the elderly,[45] or reducing the risk of fragility fractures.[46,47]

Initial treatment of vitamin D deficiency, 25(OH)D < 20 ng/mL (50 nmol/L), requires 50,000 IU of vitamin D2 or D3 orally once per week for 6-8 weeks, followed by 800-1,000 IU vitamin D3 daily. Serum 25(OH)D levels should be checked after the initial 8 weeks.

The recommended dosage for nutritional vitamin D insufficiency, 25(OH)D levels of 20-30 ng/dL or 50-75 nmol/L, is 800-1,000 IU vitamin D3 daily, which will normalize levels in the average adult over a period of three months, though individual patients may need higher doses.[48]

In malabsorptive states, higher dosages (10-50,000 IU D2 or D3) or treatment with hydroxylated vitamin D metabolites such as calcitriol may be necessary.[15]

Vitamin D Metabolites

Calcidiol (25 hydroxyvitamin D) and calcitriol (1,25-dihydroxyvitamin D) are available in capsules. Calcitriol is readily available in the United States in capsules of 0.25 and 0.5 µg and is most useful in patients with decreased synthesis of 1,25(OH) vitamin D, such as those with chronic renal failure.[49]

Monitoring

It is important to monitor progress and compliance with vitamin D supplementation with serum 25 hydroxyvitamin D levels because the reduction in fracture incidence occurs when mean serum concentrations exceed 75 nmol/L (about 30 ng/mL) and this change may result from both improved bone health and greater muscle strength.[20]

25(OH) vitamin D serum concentrations should be measured approximately three months after initiation of therapy and the dosage should be adjusted accordingly.[48]

Patients on calcitriol with diminished renal function must be monitored for serum calcium and phosphorus levels.[49]

Concomitant Calcium Intake

Vitamin D exerts its effect on bone predominantly by increasing the intestinal absorption of calcium. Bone effects will only become significant if there is an adequate amount of calcium intake; therefore, vitamin D should always be combined with adequate amounts of calcium. It is recommended that patients older than age 50 should maintain a calcium intake of at least 1,200 mg/d. Patients with malabsorption may require higher calcium intake.[15,50]

Toxicity

Since vitamin D is a fat-soluble vitamin and is stored in adipose tissue, the possibility of intoxication with cumulative intake is of concern, though practically and pharmacologically, it would be rare. Heaney et al, in a pharmacokinetic study of vitamin D supplementation, demonstrated that equilibrium levels of serum 25(OH)D increased with oral dosing of D3 by 0.7 nmol/L for every microgram (1 µg = 40 IU) of vitamin D3 per day. Even though patients with severely decreased 25(OH)D levels can achieve a much greater increase with values up to 2-2.5 nmol/L per microgram of vitamin D per day, patients can be safely supplemented with 800 IU of vitamin D daily as recommended in clinical studies.[51]

Of note is the fact that, for patients with sarcoidosis and other granulomatous diseases, optimal levels of 25(OH)D should be in the range of 20-30 ng/mL (50-75 nmol/L) due to autonomous elaboration of the active 1,25 dihydroxyvitamin D by macrophages.[52] Additionally, thiazide diuretics in an antihypertensive regimen may result in symptomatic hypercalcemia in combination with calcium and vitamin D supplementation.[53]

Conclusions

Vitamin D plays an important role in overall general health due to its broad endocrine and paracrine functions, particularly with regard to musculoskeletal health. Serum levels of 25(OH)D convey important information regarding body stores and clinical studies in geriatric patients have established guidelines for these levels based upon improvements in muscle strength, balance, and decreased incidence of falls and fragility fractures.

Recommendations

All geriatric patients should have an assessment of serum 25 hydroxyvitamin D levels as part of their general periodic evaluations. Vitamin D deficient and insufficient states need to be treated with high-dose vitamin D3 to optimize physical function, prevent fractures, and prevent decline in quality of life. Serum levels in the 30-40 ng/mL (75-100 nmol/L) range should be maintained with at least 700-800 IU/d of dietary vitamin D in conjunction with sensible exposure to sunlight to prevent photoaging and skin cancer. Regular physical activity and oral vitamin D intake are important adjunctive measures to optimize physical performance and quality of life for geriatric patients. Vitamin D requirements may need to be customized for individual patients depending upon their medications and medical conditions. ❖

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"WHI" Take a Multivitamin?

ABSTRACT & COMMENTARY

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Synopsis: *In the United States, approximately $23 billion are spent on multivitamins yearly. At least half of all Americans take some kind of supplement, the majority of which are multivitamin/minerals.[1] As part of the Women's Health Initiative (WHI), which looked at three overlapping trials of hormone therapy, vitamin D and calcium supplementation, and dietary modification, use of multivitamins in the 161,806 participants was also assessed for effects on risk of a variety of cancers, cardiovascular disease (CVD), and total mortality. Although the study reported that multivitamin use did not impact risk of cancer, CVD, or total mortality, the majority of users took a multivitamin/mineral that contained 100% or less of the RDA for the nutrients included. In addition, some participants took other supplements that were not included in the multivitamin data results. This part of the WHI was complicated by multiple different preparations of supplements, variable doses of a variety of nutrients, possible reporting bias by participants, and overlapping WHI studies, one which included supplementation with calcium carbonate/vitamin D and another that was a dietary modification trial. In addition to these complications, and subsequent simplification of the multivitamins taken into three broad categories, it may be that the amount of nutrients was not adequate or too variable to have an effect, or that the quality of the individual sources of the vitamins was not ideal to have an impact on the outcomes measured.*

Source: Neuhouser M, et al. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative Cohorts. *Arch Intern Med* 2009;169:294-304.

THIS STUDY WAS DONE AS PART OF THE WOMEN'S Health Initiative (WHI, www.nhlbi.nih.gov/whi/). WHI, a 15-year project that commenced in 1991, "was designed to test the effects of postmenopausal hormone therapy, dietary modification, and calcium and vitamin D supplements on heart disease, fractures, and breast and colorectal cancer."[1] The 161,808 women either participated in randomized controlled trials (three of them) or in an observational study. The controlled trials were overlapping, meaning that women could be randomized into one, two, or all three: hormone therapy trial, dietary modification trial, or the calcium/vitamin D trial. As was widely publicized in 2002, the hormone therapy arms (estrogen-alone and estrogen + progesterone) were stopped early due to increased incidence of myocardial infarction, stroke, deep venous thrombosis, increased risk of breast cancer in the estrogen + progesterone group, and possible increased risk of dementia and/or cognitive impairment.

The data from the WHI multivitamin study did not specify which women were in which WHI randomized controlled trials. However, it is important to know the design of two of those RCTs as they could have impacted the results of this multivitamin study.

The calcium and vitamin D group (CaD) included 36,282 postmenopausal women, randomized into two groups: The first took 1,000 mg of calcium carbonate and 400 IU of vitamin D daily; the second took a placebo. If women were already taking calcium supplements, they continued to take them no matter which group they were assigned to. Follow-up was 7-11 years, with the study question being whether supplementation of calcium and vitamin D reduced colorectal cancer risk and/or fractures.

In the dietary modification study, 48,835 postmenopausal women were randomized to one of two groups: dietary modification or comparison. The dietary intervention was a 20% total daily fat intake, with five or more fruit/vegetable servings/d, and six or more grains servings/d. In addition, participants self-monitored food intake and attended group nutrition meetings regularly.

As part of the data collected in the controlled and observational trials, multivitamin and supplement use were documented and categorized. The documentation was done at the yearly clinical visit for the women in the controlled trials, and at the three-year clinic visit for the women in the observational group; the women brought the bottles of vitamins and supplements they were taking and only those that were taken at least once a week were recorded. Direct transcription of the ingredients was performed with a validity study showing high correlation between doses transcribed and actual label photocopies. For study purposes, multivitamin preparations were divided into three categories according to amounts of individual nutrients: 1) multivitamins alone (10 or more vitamins and no minerals, and all nutrient levels at or below 100% of the RDA); 2) multivitamins with minerals (20-30 multivitamins and minerals, with all nutri-

ent levels at or below 100% of the RDA); and 3) stress multivitamins (multivitamins/minerals with doses of some individual nutrients greater than 100% of the RDA). Supplement mixtures that contained less than 10 vitamins or minerals, such as B complex preparations or antioxidant preparations, were not considered multivitamins. The study reported use of some individual supplements, such as calcium (including antacids), vitamin C, or vitamin E, and classified other supplements used under a separate category ("Single supplement not including C, E or calcium"), but did not specify what these supplements were. Of the 161,808 participants, 67,150 women (41.5%) used multivitamins. If women used supplements with less than 10 vitamins/minerals, that information was not included in the above totals.

After approximately eight years of follow-up in the clinical trials and observational study groups, there were 9,619 cases of breast, colorectal, endometrial, renal, bladder, stomach, lung, or ovarian cancer. There were 8,751 CVD events and 9,865 deaths. Multivariate statistical analysis showed no association of multivitamin use with cancer risk, CVD, or mortality.

■ COMMENTARY

This was an enormous study with an ambitious undertaking. For providers who know how hard it is to "get a handle" on what supplements patients are taking, imagine trying to gather and focus these data for such a large number of women. There are a number of reasons why I wouldn't toss your or your patients' multivitamin supplements in the trash just yet.

The actual amounts of nutrients that study participants were taking were quite varied, and difficult to determine. For example, if a woman was in the "multivitamin alone" category, but was also in the CaD arm of the study, she could have been taking 800 IU of vitamin D total between the two, and 1,000 mg of calcium carbonate, as long as she wasn't also taking other uncategorized supplements. If she was in the stress multivitamin category, there is no way to determine the total amounts of vitamin D without reviewing the individual transcribed records. This becomes important in determining effectiveness in cancer prevention. The consensus on how much vitamin D is needed daily is yet to be determined; amounts between 700 and 1,000 IU daily for adults will establish a favorable 25(OH)D level in approximately 50% of adults (some will require more than this dose range) to prevent fractures and decrease incidence of colorectal cancer. A study in 2006 reported that these vitamin D concentrations could not be reached in most adults with recommended daily intakes of 200 IU of vitamin D for younger adults and 600 of IU vitamin D for older adults.[2] The NIH-AARP study on dairy foods, calcium, and risk of cancer found an inverse relationship between incidence of colorectal cancer and intake of calcium (dietary and supplements) up to a total dose of 1,300 mg/d.[3] More studies that look at optimal dosing of these two important nutrients are needed.

Optimal forms and bioavailability of nutrients also need more study. Given that women were able to continue and choose their own supplements and multivitamins, there was a variety of brands included in this study. The sources of the ingredients making up the multivitamins were not addressed. The bioavailability of certain nutrients such as vitamin E vary with the type of preparation used. For example, synthetic vitamin E, which is the cheapest form of vitamin E (dl-alpha tocopherol), has less bioavailability than d-alpha tocopherol. Natural vitamin E is a mixture of eight bioactive chemicals (four tocotrienols and four tocopherols), but the majority of multivitamins only contain the alpha-tocopherol form, in a dl-alpha or a d-alpha form. It may be that without optimal forms of certain nutrients, optimal outcomes in terms of cancer prevention and other chronic diseases will not be seen in studies.

How multivitamins are taken may affect absorption of certain nutrients as well. For example, calcium carbonate was used as the form of calcium supplementation in the CaD arm of the study. In a more pH-neutral environment, calcium carbonate is more insoluble and thus not as well absorbed. It can also impair absorption of riboflavin and vitamin C. Certain foods will also impair absorption, such as cereal grains (phytic acid in the grains bind with calcium to make calcium phytate). It is unknown if participants in the study were guided as to how to take their supplements in relation to other supplements and food to optimize bioavailability.

The conclusion we can safely draw from this study is that a variety of doses of a variety of supplements and/or multivitamin/multimineral products taken in a variety of combinations by a large number of women undergoing a variety of other study interventions at the same time do not seem to have an effect on cancer, CVD, or mortality. More studies are needed to determine optimal doses and forms of multivitamin preparations to adequately determine outcomes on chronic diseases, cancer, and mortality. ❖

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Making the Glycemic Index More Palatable

ABSTRACT & COMMENTARY

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Synopsis: *In patients with stable type 2 diabetes, a low-glycemic index diet for six months gave a modestly better reduction in HbA1c concentration compared to a high-cereal fiber diet. A high withdrawal rate raises questions about the practicality of adhering to the diet.*

Source: Jenkins DJ, et al. Effect of a low-glycemic index or a high-cereal fiber diet on type 2 diabetes: A randomized trial. *JAMA* 2008;300:2742-2753.

CLINICAL TRIALS USING ANTIHYPERGLYCEMIC MEDICATIONS to improve glycemic control have not demonstrated the anticipated cardiovascular benefits. Low-glycemic index diets may improve both glycemic control and cardiovascular risk factors for patients with type 2 diabetes, but debate over their effectiveness continues due to trial limitations. The objective of this study was to test the effects of low-glycemic index diets on glycemic control and cardiovascular risk factors in patients with type 2 diabetes.

The investigators conducted a randomized, parallel-group study at a Canadian university hospital research center with 210 type 2 diabetics treated with antihyperglycemic medications. Subjects were recruited by newspaper advertisement and randomly assigned to one of two treatment arms (a high-cereal fiber diet or low-glycemic index dietary advice) for six months. The main outcome measure was absolute change in glycated hemoglobin A1c (HbA1c), with fasting blood glucose and cardiovascular disease risk factors as secondary measures.

In the intention-to-treat analysis, HbA1c decreased by -0.18% absolute HbA1c units (95% confidence interval [CI], -0.29% to -0.07%) in the high-cereal fiber diet compared with -0.50% absolute HbA1c units (95% CI, -0.61% to -0.39%) in the low-glycemic index diet ($P <$ 0.001). There was also an increase of high-density

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Objectives

After completing the program, physicians will be able to:

a. present evidence-based clinical analyses of commonly used alternative therapies;
b. make informed, evidence-based recommendations to clinicians about whether to consider using such therapies in practice; and
c. describe and critique the objectives, methods, results and conclusions of useful, current, peer-reviewed clinical studies in alternative medicine as published in the scientific literature.

CME Questions

13. Advancing age is associated with decreased skin production of vitamin D3.
a. True
b. False

14. Obesity is a risk factor for vitamin D deficiency.
a. True
b. False

15. Cutaneous vitamin D production is dependent upon:
a. time of day.
b. season.
c. skin pigmentation.
d. geographic latitude.
e. All of above

16. Which of the following is a minimal dose of vitamin D for reducing fracture risk?
a. 200 IU/d
b. 400 IU/d
c. 600 IU/d
d. 700-800 IU/d

Answers: 13. a, 14. a, 15. e, 16. d.

lipoprotein cholesterol in the low-glycemic index diet of 1.7 mg/dL (95% CI, 0.8-2.6 mg/dL) compared with a decrease of high-density lipoprotein cholesterol by -0.2 mg/dL (95% CI, -0.9 to 0.5 mg/dL) in the high-cereal fiber diet ($P = 0.005$). The reduction in dietary glycemic index related positively to the reduction in HbA1c concentration ($r = 0.35$; $P < 0.001$) and negatively to the increase in high-density lipoprotein cholesterol ($r = -0.19$; $P = 0.009$).

In patients with type 2 diabetes, six-month treatment with a low-glycemic index diet resulted in moderately lower HbA1c levels compared to a high-cereal fiber diet.

■ COMMENTARY

Diet and lifestyle changes have been shown to effectively prevent or help manage type 2 diabetes in high-risk patients. Such patients are also at risk for cardiovascular diseases. Controversy exists as to whether medications and diets that improve glycemic control in such patients also improve cardiovascular outcomes. The World Health Organization and the Diabetes Associations of the United States, Canada, and the United Kingdom have given qualified support for the glycemic index concept, but many health professionals consider the index too complex and variable for use in clinical practice.[1]

Glycemic index is a method of ranking carbohydrates from 0 to 100 based on the extent to which they raise blood sugar levels immediately after eating compared to reference foods. High-glycemic index foods lead to a peak in blood sugar within 30-60 minutes of eating, followed by a rapid decline. Low-glycemic index foods usually have a later and lower peak, spread out over up to two hours.

A new and more complete set of glycemic index tables was published at the end of 2008.[1] Low-glycemic index foods have a score of 55 or less when compared to glucose as the reference food (bread is another common reference standard). Common foods with low scores include most varieties of legumes, pasta, fruits, and dairy products. Part of the practical difficulty with this index is that breads, breakfast cereals, rice, and snack products, including whole-grain versions, are available in high-glycemic index forms (70 or greater) and low-scoring forms. However, many manufacturers do not put these values on their labels, and the values can vary from country to country. Highly processed, convenience, and sugary foods tend to have high-glycemic index values.

The glycemic index should not be used in isolation. For example, chocolate has a low-glycemic index, but its high saturated fat content must also be taken into consideration.

Low-glycemic index diets are claimed to improve both glycemic control and cardiovascular risk factors. A 2009 Cochrane systematic review of trials using a low glycemic index diet found reduced levels of glycated proteins in diabetes patients.[2] The clinical trial reviewed here sought to address questions regarding the impact of a low-glycemic index diet on cardiovascular risk factors. Previous trials have reported conflicting results, although these were generally of shorter duration and enrolled small numbers of patients. The trial reviewed here sought to correct this by enrolling more than 200 participants and being conducted over six months. The participants had stable type 2 diabetes with HbA1c concentrations between 6.5% and 8.0%. A previous one-year trial of a low-glycemic diet that found no beneficial effect on HbA1c levels was criticized for enrolling participants with a mean concentration of 6.1%, thus making it difficult to detect beneficial reductions.[3] Participants in the trial being reviewed here were taking oral antihyperglycemic medications. Those taking acarbose were ineligible. Acarbose is an alpha-glucosidase inhibitor that is required for carbohydrate digestion; it basically creates a low-glycemic index diet by slowing the rate of carbohydrate absorption from the intestinal tract.

The participants were randomly assigned to a low-glycemic index diet or a diet high in cereal fiber. The carbohydrate servings were calculated to deliver 42%-43% of total dietary calories. Different calorie totals were permitted based on participants' weight-loss goals. Although participants were informed this was not a weight-loss trial, most began the trial overweight and wished to lose weight. Participants were given lists of either low-glycemic index foods or high-cereal fiber foods. Daily records of food intake were maintained. Monthly visits were scheduled to check on participants' compliance with their assigned diet.

The study adhered to high standards in reporting. Power calculations were presented, along with an unplanned interim analysis. While conducting the trial, a new report demonstrated a smaller than anticipated HbA1c reduction from a similar diet. The interim analysis found a similarly small reduction, allowing the researchers to revise their power analysis and increase the number of participants required. Several statistical tests were conducted to check for various confounding variables. One limitation with this trial was the high drop-out rate (21%), although this is comparable to similar studies.

Results were analyzed on an intention-to-treat basis. As listed above, significantly greater improvements were found for the low-glycemic index diet in HbA1c

and HDL levels, but no significant differences in LDL or total cholesterol levels. The two diets did not differ significantly in their impact on blood pressure or C-reactive protein.

This well-conducted trial provides further evidence for the effectiveness of low-glycemic index diets in improving glycemic control and reducing certain cardiovascular disease risk factors. Although the reduction in HbA1c concentration was modest, the authors concluded that it was clinically significant. The reduction falls within the range given by the FDA as clinically meaningful in the development of new medications. Guiding diabetic patients on selecting low-glycemic index foods thus can be helpful as part of overall management of type 2 diabetes. ❖

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News Brief

NIH Announces Challenge Grants in Health and Science Research

THE NATIONAL INSTITUTES OF HEALTH (NIH) HAS received new funds for Fiscal Years (FYs) 2009 and 2010 as part of the American Recovery & Reinvestment Act of 2009. The NIH has designated at least $200 million in FYs 2009 and 2010 for a new initiative called the NIH Challenge Grants in Health and Science Research.

The NIH has identified a range of Challenge Areas that focus on specific knowledge gaps, scientific opportunities, new technologies, data generation, or research methods that would benefit from an influx of funds to quickly advance the area in significant ways. Each NIH institute, center, and office — including the National Center for Complementary and Alternative Medicine (NCCAM) — has selected specific Challenge Topics within the broad Challenge Areas related to its mission.

NIH anticipates funding 200 or more grants, each of up to $1 million in total costs, pending the number and quality of applications and availability of funds. In addition, Recovery Act funds allocated to NIH specifically for comparative effectiveness research (CER) may be available to support additional grants. Projects receiving these funds will need to meet this definition of CER: "a rigorous evaluation of the impact of different options that are available for treating a given medical condition for a particular set of patients. Such a study may compare similar treatments, such as competing drugs, or it may analyze very different approaches, such as surgery and drug therapy." Such research may include the development and use of clinical registries, clinical data networks, and other forms of electronic health data that can be used to generate or obtain outcomes data as they apply to CER. The application due date is April 27. 2009.

For general information on NCCAM's implementation of NIH Challenge Grants, contact: Richard Nahin, PhD, MPH, Acting Director, Division of Extramural Research, NCCAM, NIH, (301) 496-7801, nahinr@mail.nih.gov. For financial or grants management questions, contact: George Tucker, Director, Office of Grants Management, NCCAM, NIH, (301) 451-6330, tuckerg@mail.nih.gov. ❖

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