

Vitamin D Goal Likely to Double for Older Adults

BY SHERRY BOSCHERT

SAN FRANCISCO — The first update in recommendations for dietary intake of vitamin D since 1997 is expected in May and probably will comprise a conservative change from the status quo, according to one expert.

The Institute of Medicine's Food and Nutrition Board has been reviewing the literature, including consideration of as-

sociations between serum vitamin D levels and disease indicators. "The grapevine says they are going to come in very conservative. They are going to require evidence from randomized, controlled trials, and those don't really exist today," Dr. Neil Binkley said at a meeting sponsored by the American Diabetes Association.

The current Dietary Reference Intake (or Recommended Dietary Allowance) describes "adequate" intake as 200 IU/day

for people up to age 50 years, 400 IU/day for those aged 51-70 years, and 600 IU/day for people older than 70 years.

Dr. Binkley of the University of Wisconsin, Madison, expects the new intake recommendation for older adults to roughly double from 400 IU/day to 800 or maybe 1,000 IU/day.

"This will be an evolution," he said. "I think the next iteration coming out in May is going to be a step up, but it's prob-

ably not going to get us all the way there."

Recent data suggest that much higher levels should be consumed daily to keep serum 25-hydroxyvitamin D levels (25[OH]D) in desired ranges, he explained. Generally, levels lower than 10 ng/mL indicate vitamin D deficiency, 10-30 ng/mL reflects vitamin D insufficiency, and a 25(OH)D level above 30 ng/mL is considered optimal.

Optimal levels may differ by bodily system, he noted. Serum 25(OH)D levels greater than 40 ng/mL may be best for bone health, while leg function appears to be better with levels above 38 ng/mL. But a level above 36 ng/mL has been associated with reduced risk for colorectal cancer, and levels of 36-40 ng/mL have

effect, Intentional Injury, Retroperitoneal Fibrosis, Shock. Cardiovascular System – *Infrequent*: Deep thrombophlebitis, Heart failure, Hypotension, Postural hypotension, Retinal vascular disorder, Syncope; *Rare*: ST Depressed, Ventricular Fibrillation. Digestive System – *Frequent*: Gastroenteritis, Increased appetite; *Infrequent*: Cholecystitis, Cholelithiasis, Colitis, Dysphagia, Esophagitis, Gastritis, Gastrointestinal hemorrhage, Melena, Mouth ulceration, Pancreatitis, Rectal hemorrhage, Tongue edema; *Rare*: Aphthous stomatitis, Esophageal Ulcer, Periodontal abscess. Hemic and Lymphatic System – *Frequent*: Echinomys; *Infrequent*: Anemia, Eosinophilia, Hypochromic anemia, Leukocytosis, Leukopenia, Lymphadenopathy, Thrombocytopenia; *Rare*: Myelofibrosis, Polycythemia, Prothrombin decreased, Purpura, Thrombocytopenia. Metabolic and Nutritional Disorders – *Rare*: Glucose Tolerance Decreased, Urate Crystalluria. Musculoskeletal System – *Frequent*: Arthralgia, Leg cramps, Myalgia, Myasthenia; *Infrequent*: Arthritis; *Rare*: Chondrodystrophy, Generalized Spasm. Nervous System – *Frequent*: Anxiety, Depersonalization, Hypertonia, Hypesthesia, Libido decreased, Nystagmus, Paresthesia, Stupor, Twitching; *Infrequent*: Abnormal dreams, Agitation, Apathy, Aphasia, Circumoral paresthesia, Dysarthria, Hallucinations, Hostility, Hyperalgesia, Hyperesthesia, Hyperkinesia, Hypokinesia, Hypotonia, Libido increased, Myoclonus, Neuralgia; *Rare*: Addiction, Cerebellar syndrome, Cogwheel rigidity, Coma, Delirium, Delusions, Dysautonomia, Dyskinesia, Dystonia, Encephalopathy, Extrapyramidal syndrome, Guillain-Barré syndrome, Hypalgesia, Intracranial hypertension, Manic reaction, Paranoid reaction, Peripheral neuritis, Personality disorder, Psychotic depression, Schizophrenic reaction, Sleep disorder, Torticollis, Trismus. Respiratory System – *Rare*: Apnea, Atelectasis, Bronchiolitis, Hiccup, Laryngismus, Lung edema, Lung fibrosis, Yawn. Skin and Appendages – *Frequent*: Pruritus; *Infrequent*: Alopecia, Dry skin, Eczema, Hirsutism, Skin ulcer, Urticaria, Vesiculobullous rash; *Rare*: Angioedema, Exfoliative dermatitis, Lichenoid dermatitis, Melanosis, Nail Disorder, Peticular rash, Purpuric rash, Pustular rash, Skin atrophy, Skin necrosis, Skin nodule, Stevens-Johnson syndrome, Subcutaneous nodule. Special senses – *Frequent*: Conjunctivitis, Diplopia, Otitis media, Tinnitus; *Infrequent*: Abnormality of accommodation, Blepharitis, Dry eyes, Eye hemorrhage, Hyperacusis, Photophobia, Retinal edema, Taste loss, Taste perversion; *Rare*: Anisocoria, Blindness, Corneal ulcer, Exophthalmos, Extraocular palsy, Iritis, Keratitis, Keratoconjunctivitis, Miosis, Mydriasis, Night blindness, Ophthalmoplegia, Optic atrophy, Papilledema, Parosmia, Ptosis, Uveitis. Urogenital System – *Frequent*: Anorgasmia, Impotence, Urinary frequency, Urinary incontinence; *Infrequent*: Abnormal ejaculation, Albuminuria, Amenorrhea, Dysmenorrhea, Dysuria, Hematuria, Kidney calculus, Leukorrhea, Menorrhagia, Metrorrhagia, Nephritis, Oliguria, Urinary retention, Urine abnormality; *Rare*: Acute kidney failure, Balanitis, Bladder Neoplasm, Cervicitis, Dyspareunia, Epididymitis, Female lactation, Glomerulitis, Ovarian disorder, Pyelonephritis.

Comparison of Gender and Race The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

Post-marketing Experience The following adverse reactions have been identified during postapproval use of LYRICA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Nervous System Disorders – Headache. Gastrointestinal Disorders – Nausea, Diarrhea.

DRUG INTERACTIONS

Since LYRICA is predominantly excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), and does not bind to plasma proteins, its pharmacokinetics are unlikely to be affected by other agents through metabolic interactions or protein binding displacement. *In vitro* and *in vivo* studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between LYRICA and commonly used antiepileptic drugs. **Pharmacodynamics** Multiple oral doses of LYRICA were co-administered with oxycodone, lorazepam, or ethanol. Although no pharmacokinetic interactions were seen, additive effects on cognitive and gross motor functioning were seen when LYRICA was co-administered with these drugs. No clinically important effects on respiration were seen.

USE IN SPECIFIC POPULATIONS

Pregnancy Pregnancy Category C. Increased incidences of fetal structural abnormalities and other manifestations of developmental toxicity, including lethality, growth retardation, and nervous and reproductive system functional impairment, were observed in the offspring of rats and rabbits given pregabalin during pregnancy, at doses that produced plasma pregabalin exposures (AUC) ≥ 5 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. When pregnant rats were given pregabalin (500, 1250, or 2500 mg/kg) orally throughout the period of organogenesis, incidences of specific skull alterations attributed to abnormally advanced ossification (premature fusion of the jugal and nasal sutures) were increased at ≥ 1250 mg/kg, and incidences of skeletal variations and retarded ossification were increased at all doses. Fetal body weights were decreased at the highest dose. The low dose in this study was associated with a plasma exposure (AUC) approximately 17 times human exposure at the MRD of 600 mg/day. A no-effect dose for rat embryo-fetal developmental toxicity was not established. When pregnant rabbits were given LYRICA (250, 500, or 1250 mg/kg) orally throughout the period of organogenesis, decreased fetal body weight and increased incidences of skeletal malformations, visceral variations, and retarded ossification were observed at the highest dose. The no-effect dose for developmental toxicity in rabbits (500 mg/kg) was associated with a plasma exposure approximately 16 times human exposure at the MRD. In a study in which female rats were dosed with LYRICA (50, 100, 250, 1250, or 2500 mg/kg) throughout gestation and lactation, offspring growth was reduced at ≥ 100 mg/kg and offspring survival was decreased at ≥ 250 mg/kg. The effect on offspring survival was pronounced at doses ≥ 1250 mg/kg, with 100% mortality in high-dose litters. When offspring were tested as adults, neurobehavioral abnormalities (decreased auditory startle responding) were observed at ≥ 250 mg/kg and reproductive impairment (decreased fertility and litter size) was seen at 1250 mg/kg. The no-effect dose for pre- and postnatal developmental toxicity in rats (50 mg/kg) produced a plasma exposure approximately 2 times human exposure at the MRD. There are no adequate and well-controlled studies in pregnant women. LYRICA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. To provide information regarding the effects of in utero exposure to LYRICA, physicians are advised to recommend that pregnant patients taking LYRICA enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. This can be done by calling the toll free number 1-888-233-2334, and must be done by patients themselves. Information on the registry can also be found at the website <http://www.aedpregnancyregistry.org/>. **Labor and Delivery** The effects of LYRICA on labor and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥ 50 times the mean human exposure (AUC₀₋₂₄) of 123 $\mu\text{g}\cdot\text{hr}/\text{mL}$ at the maximum recommended clinical dose of 600 mg/day. **Nursing Mothers** It is not known if pregabalin is excreted in human milk; it is, however, present in the milk of rats. Because many drugs are excreted in human milk, and because of the potential for tumorigenicity shown for pregabalin in animal studies, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use** The safety and efficacy of pregabalin in pediatric patients have not been established. In studies in which pregabalin (50 to 500 mg/kg) was orally administered to young rats from early in the postnatal period (Postnatal Day 7) through sexual maturity, neurobehavioral abnormalities (deficits in learning and memory, altered locomotor activity, decreased auditory startle responding and habituation) and reproductive impairment (delayed sexual maturation and decreased fertility in males and females) were observed at doses ≥ 50 mg/kg. The neurobehavioral changes of acoustic startle persisted at ≥ 250 mg/kg and locomotor activity and water maze performance at ≥ 500 mg/kg in animals tested after cessation of dosing and, thus, were considered to represent long-term effects. The low effect dose for developmental neurotoxicity and reproductive impairment in juvenile rats (50 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately equal to human exposure at the maximum recommended dose of 600 mg/day. A no-effect dose was not established. **Geriatric Use** In controlled clinical studies of LYRICA in fibromyalgia, 106 patients were 65 years of age or older. Although the adverse reaction profile was similar between the two age groups, the following neurological adverse reactions were more frequent in patients 65 years of age or older: dizziness, vision blurred, balance disorder, tremor, confusional state, coordination abnormal, and lethargy. LYRICA is known to be substantially excreted by the kidney, and the risk of toxic reactions to LYRICA may be greater in patients with impaired renal function. Because LYRICA is eliminated primarily by renal excretion, the dose should be adjusted for elderly patients with renal impairment.

DRUG ABUSE AND DEPENDENCE

Controlled Substance LYRICA is a Schedule V controlled substance. LYRICA is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behavior). **Abuse** In a study of recreational users (N=15) of sedative/hypnotic drugs, including alcohol, LYRICA (450 mg, single dose) received subjective ratings of "good drug effect," "high" and "liking" to a degree that was similar to diazepam (30 mg, single dose). In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse reaction, though in some patient populations studied, this reporting rate was higher and ranged from 1 to 12%. **Dependence** In clinical studies, following abrupt or rapid discontinuation of LYRICA, some patients reported symptoms including insomnia, nausea, headache or diarrhea [see *Warnings and Precautions*], suggestive of physical dependence.

OVERDOSAGE

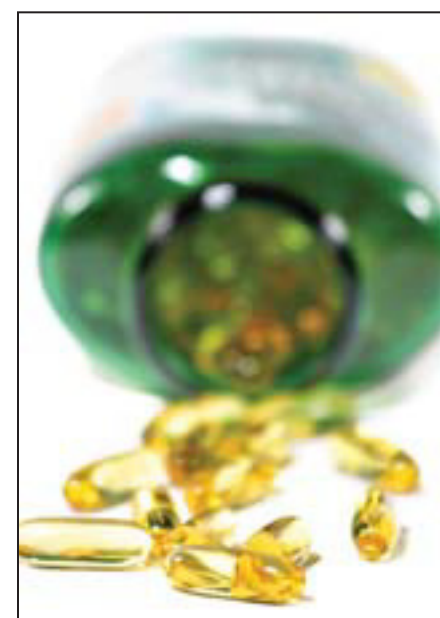
Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans There is limited experience with overdose of LYRICA. The highest reported accidental overdose of LYRICA during the clinical development program was 8000 mg, and there were no notable clinical consequences. In clinical studies, some patients took as much as 2400 mg/day. The types of adverse reactions experienced by patients exposed to higher doses (≥ 900 mg) were not clinically different from those of patients administered recommended doses of LYRICA. **Treatment or Management of Overdose** There is no specific antidote for overdose with LYRICA. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric

lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with LYRICA. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment. Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours).

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility Carcinogenesis: A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000, or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. No evidence of carcinogenicity was seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150, or 450 mg/kg in males and 100, 300, or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. **Mutagenesis** Pregabalin was not mutagenic in bacteria or in mammalian cells *in vitro*, was not clastogenic in mammalian systems *in vitro* and *in vivo*, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes. **Impairment of Fertility** In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights, and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day. In addition, adverse reactions on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD. In a fertility study in which female rats were given pregabalin (500, 1250, or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses, and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. **Human Data** In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin at a dose of 600 mg/day. After 3 months of treatment (one complete sperm cycle), the difference between placebo- and pregabalin-treated subjects in mean percent sperm with normal motility was <4% and neither group had a mean change from baseline of more than 2%. Effects on other male reproductive parameters in humans have not been adequately studied.

Animal Toxicology and/or Pharmacology **Dermatopathy** Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies. **Ocular Lesions** Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥ 2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year.



The IOM's intake recommendation could go to 800 or 1,000 IU/day.

been associated with lower risk for periodontal disease.

One study calculated that 2,600 IU/day of vitamin D supplementation would be needed to ensure that 97.5% of older women have 25(OH)D levels at or above desirable levels (J. Nutr. 2006;136:1123-26). Other experts recommend that between 2,000 and 4,000 IU/day be consumed to reduce risks for cancer and autoimmune disease, Dr. Binkley said.

He aims for levels above 40 ng/mL in his patients to consistently hit targets above 30 ng/mL, he said. As a general rule of thumb, for every 1,000 IU of supplemental vitamin D₃ ingested, circulating 25(OH)D goes up by roughly 6 ng/mL, he said.

For a patient with a serum 25(OH)D level of 20 ng/mL, taking 2,000 IU/day of vitamin D₃ would boost serum levels to about 32 ng/mL, and more than 3,000 IU/day would be needed to reach 40 ng/mL. People are unlikely to get adequate vitamin D from sunlight, and fortified foods contain roughly 40-100 IU per serving. "If we truly do need 1,000, 2,000 or 4,000 IU/day, that means you'd need to drink between 10 and 40 glasses of milk per day to get your vitamin D requirement" at current levels of food fortification, he said.

"I'm hopeful that after the Institute of Medicine's recommendation is published, we'll see a lot of people taking more vitamin D. It's a simple, safe, and effective way to improve bone health and reduce the risk of falls and fractures." *Continued on following page*



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Many Unaware of Their High Risk for Diabetes

BY SHARON WORCESTER

Although nearly a third of U.S. adults were at high risk for developing type 2 diabetes in 2005-2006, about 7% knew of their risk status, and only about half of those said they adopted risk-reduction behaviors, data from the 2005-2006 National Health and Nutrition Examination Survey suggest.

Furthermore, of those who were aware of their risk status and who received health care in the year prior to the survey, only 35% said they were advised by their physician to try to control or lose weight, 37% said they were advised to reduce fat or calorie intake, and 39% said they were advised to increase physical activity, Linda S. Geiss of the Centers for Disease Control and Prevention, Atlanta, and her colleagues reported.

The data—from 1,391 adults aged 20 years and older without diabetes who participated in the survey—showed that reports of physician advice were strongly associated with reports of engaging in risk-reduction behaviors in the past year. Of those receiving physician advice about weight loss or control, diet, and physical activity, 75%, 82%, and 71%, respectively, reported following the advice, the investigators said (*Am. J. Prev. Med.* 2010 April [doi: 10.1016/j.amepre.2009.12.029]).

The multivariate adjusted prevalence of trying to control or lose weight, reduce fat or calorie intake, and increase physical activity for those who received advice vs. those who did not was 71.0 vs.

44.2, 81.2 vs. 42.3, and 67.9 v. 38.4 for each behavior, respectively, they found.

The findings are important because prevention trials consistently show that diabetes risk can be reduced substantially through modest weight loss and increased physical activity. However, improved efforts on the part of physicians to advise patients about lifestyle modifications are likely to be insufficient for addressing the problem of suboptimal

adoption of risk-reduction behaviors, the investigators argue.

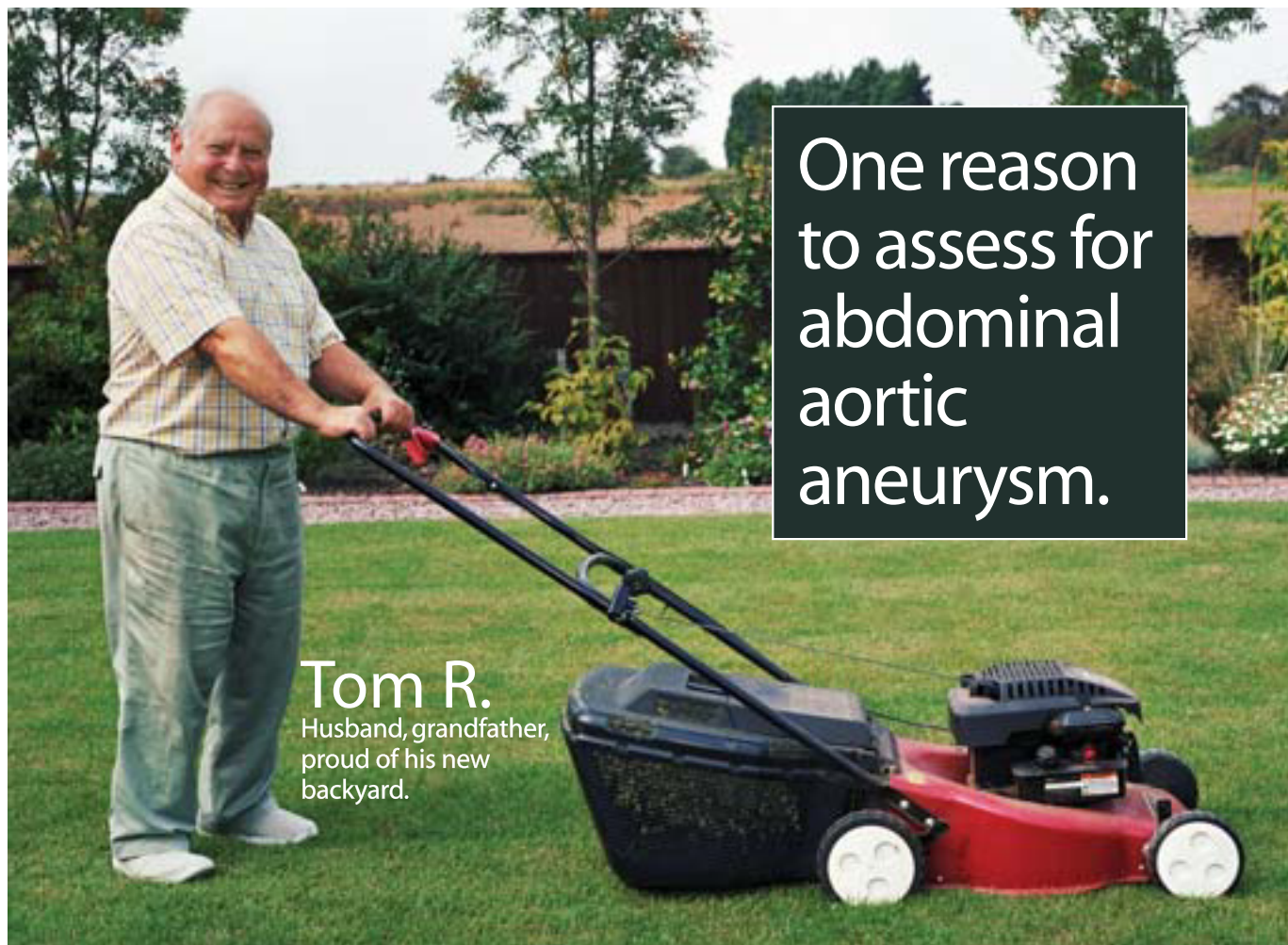
Although physician advice has been shown to help initiate changes in health behaviors, it has not been shown to be associated with maintaining the changes, they explained.

“Prevention promotion by physicians and other health professionals may be more effective if part of a larger process within healthcare systems and commu-

nities to promote behavior change, and pragmatic approaches for linking primary care with effective community-based approaches are needed,” they wrote.

They went on to say that prospective studies of interventions and policies to promote and maintain healthy lifestyles with more objective measures of behaviors and outcomes are needed.

The investigators reported no financial disclosures. ■



Continued from previous page

Medicine meets, food fortification will go up,” he added.

The American Academy of Pediatrics in 2008 recommended that children and adolescents get 400 IU/day of vitamin D, double the current Dietary Reference Intake. The National Osteoporosis Foundation recommends that people up to age 50 ingest 400-800 IU/day, and that adults aged 50 or older get 800-1,000 IU/day.

Observational studies suggest that low vitamin D levels are associated with increased risk for diabetes. Several studies found that children who received vitamin D supplementation had a lower risk for developing type 1 diabetes, and the Nurses Health Study found an association between low vitamin D status and higher risk for type 2 diabetes over 20 years of follow-up.

Two prospective studies with 36 patients each found no significant effect of vitamin D supplementation on diabetes risk, but these studies were too small, Dr. Binkley said. A post hoc analysis of a randomized, controlled trial of 800 IU/day of vitamin D for fracture prevention in 3,314 women over age 70 found no protective effect against development of type 2 diabetes, but compliance with vitamin D supplements was poor, he noted (*Age Ageing* 2009;38:606-9).

Dr. Binkley said he has no conflicts of interest related to these topics. ■

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Reference: 1. Reardon RF, Cook T, Plummer D. Abdominal Aortic Aneurysm. In: Ma OJ, Mateer JR, Blaivas M, eds. Emergency Ultrasound. 2nd ed. New York, NY: McGraw-Hill; 2008: 149-168. AortaScan and Verathon are trademarks of Verathon Inc. © 2010 Verathon Inc. 1001FPN-Ad 0900-2989-00-86

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