

# Upper Intake Level for Vitamin D Seen as Too Low

BY JEFF EVANS  
Senior Writer

ARLINGTON, VA. — The currently recommended tolerable upper intake level of vitamin D is too low and is hindering clinical research efforts to determine a more accurate optimal intake of the vitamin, said Reinhold Vieth, Ph.D., at a conference sponsored by the American Society for Bone and Mineral Research.

Preliminary research and case reports on the use of high doses of vitamin D suggest that the tolerable upper intake level (UL) could be much higher than it now is, yet some researchers think that higher doses will cause hypercalcemic toxicity, according to Dr. Vieth, director of the bone and mineral laboratory at Mount Sinai Hospital, Toronto.

The lowest adverse-event level for vitamin D intake was established at 3,800 IU/day because of a 1984 study in which six patients developed hypercalcemia at that level. In the same study, a dosage of 2,400 IU/day of vitamin D resulted in a statistically significant increase in serum calcium levels, but was not regarded as hypercalcemic and was considered safe. But because of an uncertainty factor of about 400 IU/day, the UL—defined as the highest level of daily vitamin D intake likely to pose no risk of adverse effects in almost all individuals in the general population—became 2,000 IU/day (50 mcg/day), Dr. Vieth said (*J. Am. Diet. Assoc.* 1998;98:699-706).

Research on the effects of vitamin D has been driven by the 2,000 IU/day UL rather than by a more careful dose-finding study of when toxicities begin to appear, he said.

There is no recommended dietary allowance (RDA) for vitamin D because when RDAs were established in 1995, there was perceived to be not enough evidence to recommend one, so an adequate intake level was “guesstimated,” Dr. Vieth said.

Vitamin D and its metabolites are stored at their high-

est concentration in adipose tissue, but a roughly equal amount overall is stored in muscles, contrary to what has been published. This leaves a large reservoir to store vitamin D. If one extrapolates a study of vitamin D toxicity in rats to humans, the highest dosage that did not cause hypercalcemia was equivalent to 5,000 IU/kg per day; hypercalcemia began to occur when the serum 25-hydroxyvitamin D (25[OH]D) level reached an equivalent of 2,000 nmol/L (*Arch. Biochem. Biophys.* 1980;202:43-53).

Perhaps the best study of vitamin D toxicity in humans is a report of a family that stole a container from a shipping dock of what they thought was vegetable oil but was actually a concentrate of vitamin D that was for veterinary use, according to Dr. Vieth (*Ann. Intern. Med.* 1995;122:511-3). In the family, hypercalcemia began to occur at serum 25(OH)D levels that were well above the reference range upper limit of 500 nmol/L; their serum 25(OH)D concentrations ranged from 847 nmol/L to 1,652 nmol/L.

Normally the vitamin D-binding protein binds more than 99% of all 1,25-dihydroxyvitamin D (1,25[OH]<sub>2</sub>D) and only a “very small proportion” of vitamin D metabolites. But more than 1% of 1,25(OH)<sub>2</sub>D was unbound from the binding protein in the family members and more of it was effectively displaced from the protein than normal because of the relatively high level of vitamin D metabolites in the patients. The levels of total 1,25(OH)<sub>2</sub>D were just high-normal in the family members, but most had a high level of unbound 1,25(OH)<sub>2</sub>D. This suggests that the likely mechanism through which vitamin D causes toxicity is the displacement of 1,25(OH)<sub>2</sub>D from vitamin D-binding protein, Dr. Vieth said.

The capacity of vitamin D-binding protein for all

metabolites of vitamin D is 4,000-5,000 nmol/L, but when concentrations of 25(OH)D approach 1,000 nmol/L, vitamin D-binding protein cannot bind as much 1,25(OH)<sub>2</sub>D, he said.

“One problem with the vitamin D nutrition story is that we start to think of it as a drug, something to be used in treatment. Unlike any other drug I’m aware of, there’s never been a dose-finding study done,” said Dr. Vieth, who is also a professor in the departments of nutritional sciences, pathology, and laboratory medicine at the University of Toronto.

In a preliminary study of 12 patients with active-phase multiple sclerosis, Dr. Vieth and his colleagues studied the safety of using up to 40,000 IU/day of vitamin D<sub>3</sub> in treatment. The dosage of vitamin D<sub>3</sub> in the study increased from 4,000 IU/day up to 40,000 IU/day during the course of the study.

Many of the patients had already been taking vitamin D supplements; they had baseline concentrations of 100 nmol/L of 25(OH)D. The patients also received about 1,000

mg/day of calcium phosphate.

“So if you’ve got a cohort that’s going to be susceptible to vitamin D toxicity in a phase I study, this is it,” he said.

No events of hypercalcemia and no change in urinary calcium levels have occurred. The investigators have received funding to extend the study.

With the results of his study and after a review of the literature, Dr. Vieth concluded that about 1 mg/day or 40,000 IU/day of vitamin D<sub>3</sub> might be the threshold at which toxicity begins.

But the actual UL for vitamin D should be about 10,000 IU/day, or 250 mcg/day, Dr. Vieth suggested. This is not an RDA, but it is a level not likely to cause harm in most individuals. ■

**‘There is no RDA for vitamin D because when RDAs were established in 1995, there was perceived to be not enough evidence to recommend one.’**

## Vitamin D Deficit May Explain Many ‘Age-Related’ Morbidities

BY JEFF EVANS  
Senior Writer

ARLINGTON, VA. — Inadequate levels of vitamin D may help to explain not only morbidities such as osteoporosis but also less-appreciated effects of vitamin D insufficiency that worsen bodily functions and are commonly thought to be related to aging alone, Dr. Neil Binkley reported at a conference sponsored by the American Society for Bone and Mineral Research.

“I would like to suggest to you that vitamin D inadequacy might be contributing to what we are currently accepting as old age-related morbidity,” said Dr. Binkley, codirector of the University of Wisconsin Osteoporosis Clinical Center and Research Program, Madison.

The prevalence of densitometric osteopenia markedly increases with advancing age, and at any given bone density, age has a “profound impact” on the risk of fracture, he said.

But many other conditions that are affected by vitamin D status have been labeled as “age-related” morbidities, including sarcopenia, falling, overactive bladder, swallowing dysfunction, decreased lung function, macular degeneration, and cognitive decline.

“Always consider that perhaps some of these other age-related morbidities are

what are causing this dramatic effect of age on fracture,” Dr. Binkley said.

► **Sarcopenia.** The expression of vitamin D receptors declines in muscle with aging. In muscle, vitamin D also may be involved with calcium transport and actin-myosin interaction.

A study of 1,008 older adults has suggested that vitamin D inadequacy is associated with sarcopenia. After a 3-year follow-up, men and women with baseline 25(OH)D levels less than 25 nmol/L were more than twice as likely to develop sarcopenia (based on either grip strength or muscle mass) than were those with a higher level of 25(OH)D.

► **Falling.** It is not known whether vitamin D status and muscle strength are causally related, but “it is, however, clear that vitamin D status is related to the risk of falling in both older men and older women,” Dr. Binkley said.

The risk of falling is increased by orthopedic disabilities, visual impairment, central or peripheral neurologic dysfunction, and muscle weakness, which may be the main risk factor, he said. A meta-analysis of double-blind, randomized, trials showed that vitamin D reduced the risk of falling by 22% (*JAMA* 2004;291:1999-2006).

► **Overactive bladder.** Bladder dysfunction also may be associated with muscle weakness, leading to poorer coordination

of the muscles used to control urination. Overactive bladder affects 30%-40% of adults older than 75 years of age and two-thirds of nursing home residents; it is defined as urinary urgency with or without incontinence, usually with frequency and nocturia.

In a study of nearly 6,000 community-dwelling women aged 40 years or older, women in the highest quintiles of vitamin D intake had the lowest risk of developing overactive bladder (*Neurourol. Urodyn.* 2004;23:204-10).

► **Difficulty swallowing.** Up to 40% of individuals older than 60 years have problems swallowing, which can lead to undernutrition, sarcopenia, and aspiration pneumonia. Dysphagia associated with aging classically has been felt to reflect neurologic disease such as Parkinson’s or stroke, but more recent work has shown that even normal healthy adults swallow more slowly and generate lower tongue pressures than do younger adults.

“I think it’s at least plausible that this decreased muscle function might be causally related to the increased risk of dysphagia observed with advancing age,” Dr. Binkley suggested.

But no research has been conducted on vitamin D status and the risk of dysphagia of aging, he said.

► **Pulmonary function.** Both the forced expiratory volume in the first second af-

ter taking a deep breath and forced vital capacity are known to decline with aging; poor results on such tests are associated with substantial morbidity and mortality.

In a study of people in the National Health and Nutrition Examination Survey III (NHANES III) who were aged 60 years or older, both of those measures of lung function were significantly higher among people in the highest quintile of serum 25(OH)D concentration than in individuals in the lowest quintile of the vitamin.

Biologically plausible ways in which vitamin D might protect against a decline in pulmonary function include the possibility of a decline in respiratory muscle function with inadequate levels of vitamin D, lung tissue remodeling, or a reduction in airway inflammation.

► **Age-related macular degeneration.** In a yet-to-be published study involving 7,752 people who participated in NHANES III, the risk of developing age-related macular degeneration declined steadily from the lowest to the highest quintiles of serum 25(OH)D concentration.

► **Dementia/cognitive decline.** In a small case-control study, deficient and extremely low levels of vitamin D were found in significantly more ambulatory women with Alzheimer’s disease than in control women of the same age without Alzheimer’s or fractures (*Bone* 1998;23:555-7). ■