

Endocrine today

CLINICAL NEWS ON DIABETES AND ENDOCRINE DISORDERS

Vitamin D: Research appears to support greater daily intake

From cancer to stroke to autoimmune diseases, research is piling up on vitamin D's potential effects.

Since its discovery in 1922, vitamin D was associated with bones and only bones. Vitamin D deficiency led to rickets in children and osteomalacia in adults, but there was little indication that it played an active part in other types of tissues or diseases.

In 1971, the active form of vitamin D, 1,25(OH)₂D₃, was discovered by the laboratory of **Anthony W. Norman, PhD**, who is currently a distinguished professor emeritus of biochemistry and biomedical sciences at the University of California, Riverside, ushering in an ongoing era of discovery. Recently, the pace of discoveries has stepped up, and the vitamin D receptor is now known to be present in over 35 tissues. Now it is known that vitamin D plays a role in conditions including cancer, heart disease and autoimmune disease, all systems that have vitamin D receptor. Because of these discoveries, and evidence that higher daily intake may be beneficial to improve bone mineral density and bolster the immune system, some experts are calling for substantial increases in the recommended daily intake of the vitamin.

Keeping pace with the multitude of papers published yearly on vitamin D is difficult, but there are a number of areas of research that experts point to as particularly promising. One of these is the link between lower levels of vitamin D and myocardial infarction and stroke.

“Vascular smooth muscle has vitamin D receptors, and cardiomyocytes have vitamin D receptors,” said **Michael Holick, MD, PhD**, a professor in Boston University's department of endocrinology, diabetes and nutrition. “We think that vitamin D is playing a role in both modulating vascular tone as well as cardiomyocyte regeneration.”

This mechanism may be responsible for a remarkable increase in MI risk in people with vitamin D deficiency. In a study published in June 2008 in the *Archives of Internal Medicine*, men who were deficient (≤ 15 ng/mL) in 25-hydroxyvitamin D



Anthony W. Norman, PhD, Distinguished Professor Emeritus of Biochemistry & Biomedical Sciences at the University of California, Riverside.

(25[OH]D) — the precursor hormone to vitamin D's active form and the best indicator of vitamin D status — had a relative risk of MI of 2.42 (95% CI, 1.53-3.84) compared with those who were considered sufficient (≥ 30 ng/mL). Researchers prospectively assessed the 25(OH)D levels of 18,225 men in the Health Professionals Follow-up Study and found the increased risk remained even after adjustment for numerous confounders including family history of MI, BMI, history of diabetes and hypertension, ethnicity, cholesterol levels and triglyceride levels (adjusted RR=2.09 [95% CI, 1.24-3.54]). Men with intermediate levels of 25(OH)D also were at higher risk than those with sufficient levels.

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[What would you recommend for the appropriate daily intake of vitamin D?](#)

Another study published in September 2008 in *Stroke* showed that increasing levels of both 25(OH)D and the active form, 1,25(OH)₂D, were associated with substantially decreased risk of fatal stroke. Another June 2008 paper also published in the *Archives of Internal Medicine* showed that both cardiovascular mortality and all-cause mortality were associated with vitamin D levels among patients referred for coronary

angiography. The multivariate-adjusted HR for all-cause mortality for individuals in the lowest quartile of 25(OH)D (median 7.6 ng/mL) vs. those in the highest quartile (median 28.4 ng/mL) was 2.08 (95% CI, 1.60-2.70). For CV mortality, the HR was 2.22 (95% CI, 1.57-3.13). These associations were found to be independent of coronary artery disease, physical activity level and other confounders.

Hector DeLuca, PhD, a professor in the biochemistry department at the University of Wisconsin-Madison, said that while the data on CV outcomes and other associations are promising, it is important to remember that the vast majority of data on vitamin D is only correlative in nature. "It's starting to look impressive, but it certainly isn't cause and effect," he said.

Cancer and vitamin D

DeLuca said that another realm where this correlative data have become relatively convincing is in certain types of cancer. For example, results of a September 2008 meta-analysis published in the *Journal of Steroid Biochemistry and Molecular Biology* showed a trend toward less breast cancer among women with a daily intake of vitamin D of at least 400 IU.



**Michael
Holick**

In one of the few prospective, interventional studies of vitamin D that have been conducted outside the realm of bone health, 1,179

postmenopausal women were randomized to receive either calcium supplementation alone, calcium supplementation plus 1,100 IU vitamin D or placebo. The unadjusted RR for all cancers was 0.402 ($P=.01$) in the vitamin D group, and the RR was not significant in the calcium alone group.

Holick said that the potential for reducing risk of other specific malignancies may be substantial as well. “It has been estimated that if you increase your vitamin D intake by at least an additional 1,000 units of vitamin D per day, you reduce your risk of developing colon cancer by 50%,” he said.

FAST FACTS

Issues of Concern

- 1** Research into the action of vitamin D continues to add to a body of evidence about the effects of the vitamin on tissues and disease.
- 2** Recent research has helped elucidate the role of vitamin D in risk for MI and stroke, breast cancer, and risk of type 1 diabetes, among other diseases. The American Academy of Pediatrics now recommends 400 IU per day for children; the National Osteoporosis Foundation recommends 800 IU to 1,000 IU per day for adults over 50.
- 3** A change in adult recommendations for vitamin D intake may be coming soon. Some of the experts interviewed by ENDOCRINE TODAY stressed a need to move slowly, however, before making population interventions a reality. A randomized, controlled, long-term clinical trial of vitamin D in early CHD prevention is necessary to support the epidemiological research that has been done to date.

Autoimmune disorders

Another relatively new realm of vitamin D research is its role in autoimmune diseases. A landmark birth-cohort study of type 1 diabetes looked at mothers in a region of northern Finland who gave birth in 1966 and followed the children through 1997. Of 10,366 children studied, 81 were diagnosed with type 1 diabetes. Regular vitamin D supplementation with 2,000 IU daily during infancy was found to substantially decrease the risk of developing diabetes (RR=0.22 [95% CI, 0.05-0.89]) compared with children who had lower intake of vitamin D. Furthermore, children who were suspected of having rickets in their first year of life were three times as likely to develop diabetes compared to those with no suspicion of rickets.

“The vitamin D receptor is found in T cells and other cells of the immune system,” DeLuca said. He added that the discovery of the receptor in such diverse areas of the body has led to the explosion in research. “Finding it in these places is key to expanding our view of this substance and how it might help public health.” With regard to other autoimmune disorders, there is evidence that vitamin D may play a role in multiple sclerosis, rheumatoid arthritis and other conditions.

Vitamin D intake in children

The role in development of type 1 diabetes aside, vitamin D levels in children have long been considered a crucial part of bone development and bone health. According to **Mark A. Sperling, MD**, a professor in the department of pediatrics at the University of Pittsburgh, rickets is still an issue in northern areas of the United States and elsewhere.

“We don’t get more than half a dozen cases of rickets each year, but we shouldn’t even get that,” he said, adding that there is a need to “make people aware that there is a widespread relative deficiency of vitamin D intake throughout the population, and that it has wide benefits if taken, both for immediate bone health and for future bone health. What you lay down in your years of putting down bone is what you have when you start losing bone.”



**Mark A.
Sperling**

Rickets can also lead to other musculoskeletal problems later in life. Recently, the American Academy of Pediatrics changed its recommended intake of vitamin D in children to a minimum of 400 IU per day, up from 200 IU.

“Some of us think that even that may not be adequate and they could have been even more liberal,” said Sperling, who is also a member of the *Endocrine Today* Editorial Board. “But I do understand their cautious, conservative approach, and it’s a step in the right direction.”

The AAP has taken that step, and the National Osteoporosis Foundation has joined them by recommending 400 to 800 IU daily for adults under 50 and 800 to 1,000 IU for adults over 50 years. The U.S. government, however, has yet to change its recommendations from 200 IU, 400 IU and 800 IU for individuals up through age 50, ages 51 to 70 and older than 71 years, respectively. These recommendations were established in 1997 by a committee formed by the Institute of Medicine; a new committee has recently been formed to revise these guidelines.

Is more better?

Diseases and Conditions Potentially Affected by Vitamin D	
Condition	Potential mechanism
Myocardial Infarction, Stroke	Vitamin D receptor found in vascular smooth muscle and cardiomyocytes; renin-angiotensin regulation and coagulation response modulation could have effect.
Prostate Cancer, Breast Cancer, Colon Cancer	Vitamin D may be involved in cell cycle regulation and cell proliferation inhibition.
Type 1 Diabetes, Multiple Sclerosis	VDR found in T-cells and dendritic cells, regulating adaptive immune system response.
Rickets/Osteomalacia	Vitamin D is a regulator of calcium homeostasis, affecting bone remodeling.
Type 2 Diabetes	Vitamin D receptor found in pancreatic B-cells; play a role in mediating insulin secretion.

“The concern at the present time is that since our government’s advice about how much vitamin D we should be taking is old-fashioned and out of date, what should be the next steps?” asked Norman.

He goes on to state: “The feeling is that the experts in the vitamin D field are already recommending taking 1,000 to 2,000 or more U a day. But ideally our government needs to conduct evidence-based research first to justify a significant increase in ‘official advice’ concerning daily vitamin D intake levels for our citizens. Everyone needs to know how much vitamin D to really take on a daily basis. Is it 2,000 U a day? Or 3,000 or 4,000?”

As some experts contend that much higher intake vitamin D would be even more effective, the question of toxicity arises. Toxic levels of circulating vitamin D are commonly cited as being above 200 ng/mL, and Norman said taking several thousand IU daily will not bring blood levels close to that threshold.

“We have to be careful, because we’re sort of in a grey zone here,” he said. “We know that people really need a higher vitamin D nutritional status than they have, but they can’t go bonkers. Presently the government says that the upper safe level is 10,000 U a day. The vitamin D community ... would say that probably could go up to 50,000 and maybe even 100,000 U.”

With regard to potential negative effects outside of hypervitaminosis D and associated hypercalcemia, one study showed a slight trend toward an increased risk of aggressive prostate cancer with higher levels of vitamin D. Holick said that the men in that study also ingested close to two grams of calcium per day, and questioned the trend toward increased risk.

“We can’t fully relate the high vitamin D intake to increases in prostate cancer,” he said. “In my opinion, based on all of the data that we’ve seen to date, if anything it will decrease your risk.”

Cause for caution

Supplementing the entire population with vitamin D may seem attractive, but there are some reasons to move slowly. Norman pointed out difficulties involved with racial differences in vitamin D metabolism.

“Because of their skin color, black people don’t make anywhere near the amount of vitamin D that white people do,” he said. “It is a really complicated question to answer. When you talk about intervention, it should be one that would apply to all the ethnicities in America.”



There also remain questions of causality, with the bulk of literature taking the form of observational, correlative studies. Still, “every time we turn around, we’re finding more and more links,” said **Michael Kleerekoper, MD**, an endocrinologist at Saint Joseph Mercy Hospital in Ann Arbor, Mich.

Michael Kleerekoper “The vitamin D receptor is a ubiquitous receptor, it’s in many tissues. What we don’t know is how often it is turned on, and what level of vitamin D turns it on. But the potential for vitamin D to have an impact on many tissues is really quite remarkable,” added Kleerekoper, who is also a member of the *Endocrine Today* Editorial Board.

There are interventional studies ongoing to try and answer questions of causality. One such study is comparing no vitamin D supplementation to 1,000 IU, 2,000 IU and 4,000 IU in black men and examining the effect this has on colon and prostate cancer prevention. Researchers with another small prospective study are examining how 2,000 IU daily vitamin D might lower the risk of type 1 diabetes in children. Another randomized trial will examine the effect of 2,000 IU daily vitamin D on CV risk factors and endpoints in patients with diabetic kidney disease. There are many others as well.

With the pace of research on vitamin D clearly continuing to accelerate, Holick stressed the need and opportunity involved with this one substance.

“Globally, probably 50% of the world’s population is deficient in vitamin D,” he said. “Preventive medicine is certainly much less expensive than interventional medicine. If you could correct vitamin D deficiency, and if it was to substantially reduce the burden of many of these serious chronic diseases later in life, that would be pretty impressive.” – *by Dave Levitan*

POINT / COUNTER

[What would you recommend for vitamin D intake, and what is a safe upper limit to keep in mind?](#)

PERSPECTIVE**Early CHD prevention trial is necessary**

The essence of the vitamin D database is now such that a carefully controlled randomized large scale long-term clinical trial in early CHD prevention will be necessary to evaluate these promising findings. Without such a trial, the epidemiologic data gathered thus far is suggestive but not definitive evidence of causation linkage between vitamin D and CHD. Population interventions should not be based solely on such evidence but require more careful evaluations of the benefits and also the risks of such interventions.



**Alan J.
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– **Alan J. Garber, MD, PhD**

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