Vitamin Boost

From muscle strength to immunity, scientists find new vitamin D benefits

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First in a two-part series. Part II: "Vitamin D: What's Enough?" is available at http://www.sciencenews.org/articles/20041016/bob9.asp.

The story of vitamin D would appear simple. Take in enough sun or drink enough fortified milk to get the recommended daily amount, and you'll have strong bones. Take a supplement, if you want insurance. But recent studies from around the world have revealed that the sunshine vitamin's role in health is far more complex. More than just protecting bone, vitamin D is proving to preserve muscle strength and to give people some protection against deadly diseases including multiple sclerosis (MS), diabetes, and even cancer.

What's now clear is that vitamin D is a potent force in regulating cell growth, immunity, and energy metabolism, observes David Feldman of Stanford University School of Medicine. He's the editor of a new 1,300-page compilation of research findings from more than 100 labs working on this substance (2004, *Vitamin D*, Academic Press). Not only is the vitamin gaining increasing respect as a governor of health, he notes, but it's also serving as the model for drugs that might tame a range of recalcitrant diseases.

Ironically, observes bone-metabolism specialist Robert P. Heaney of Creighton University Medical Center in Omaha, Neb., vitamin D is a misnomer. "A vitamin is an essential food constituent that the body can't make," he explains, but people have the capacity, right in their skin, to produce all the vitamin D they need from a cholesterol-like precursor.

Once vitamin D is available, the body converts it first into 25-hydroxy vitamin D and then into 1,25-dihydroxy vitamin D (1,25-D). This final form, which is actually a hormone, is the only active variety. Researchers loosely refer to all three substances in this biochemical cascade as "vitamin D."

The human body can generate 10,000 to 12,000 international units (IU) of vitamin D from a half-hour of summer-sun exposure. The National Academies recommend that adults, depending on their age, get from 200 to 600 IU of the vitamin each day.

In practice, however, most people in the United States get a daily intake from food and sun exposure well below that recommended intake, especially during winter. People living in the United States and Europe or farther from the equator have trouble getting enough sun to maintain adequate blood concentrations of the vitamin. When people heed dermatologists' warnings about preventing skin cancer by limiting sun exposure and using sunscreen, they also reduce their vitamin D production.

By studying the subtle effects of vitamin D deficiency and boosting animals' exposure to it in laboratory tests, researchers have been slowly teasing out the vitamin's myriad benefits.

Muscling in

Leg weakness is a common symptom of severe vitamin D deficiency. Five

years ago, nutritional epidemiologist Heike A. Bischoff-Ferrari began wondering whether vitamin D affects muscle function in apparently healthy people as well. She was particularly concerned about senior citizens, who typically suffer from an inexorable muscle wasting that begins by age 40 (SN: 8/10/96, p. 90: http://www.sciencenews.org/pages/sn_arch/8_10_96/bob1.htm). So, she measured vitamin D blood concentrations in elderly men and women and found that individuals who had higher readings also had greater thigh strength.

Bischoff-Ferrari and her team at the University of Basel in Switzerland then launched an intervention trial with 122 women in their mid-80s. The researchers administered 1,200 milligrams of calcium to all the participants, and another 800 IU of vitamin D per day to half of them. At the end of 3 months, each woman was tested for leg strength and rated on how easily she could get up from a chair, walk around an object, and sit back down.

Not only did vitamin D¨Csupplemented women perform dramatically better on these tests, but they sustained only about half as many falls during the trial, according to the researchers' report in the February 2003 *Journal of Bone and Mineral Research*.

Bischoff-Ferrari, now at the Harvard Medical School in Boston, teamed with other Boston researchers to analyze past studies of falls in elderly people. Falls are a leading cause of fracture and disability in that population and account for U.S. medical bills exceeding $20 billion a year.

The researchers reevaluated five previously published vitamin D¨Csupplementation trials that together included more than 1,200 elderly people. Overall, a daily vitamin D intake of at least 400 IU cut a woman's risk of being injured in a fall by more than 20 percent, and higher doses had an even greater effect. Bischoff-Ferrari notes, "We showed that to get the best protection from falling, you likely have to get 800 units or more [daily]." She and her colleagues reported the findings in the April 28 *Journal of the American Medical Association*.

More recently, the team combed through a national diet-and-health survey of some 4,100 men and women 60 years and older. The researchers report in the September *American Journal of Clinical Nutrition* that blood concentration of vitamin D directly correlated with leg strength and function in these people.

Attack mode

Other correlations between vitamin D and health have captured researchers' attention. Kassandra L. Munger of the Harvard School of Public Health in Boston recently presented evidence of what appears to be a protective effect of vitamin D against MS. In two ongoing studies of 187,500 U.S. nurses, women getting at least 400 IU of vitamin D per day showed only 60 percent the risk of developing MS compared with women getting less of the vitamin, Munger and her colleagues reported in the Jan. 13 *Neurology*.

These findings not only confirmed a link seen earlier in animals but also fit with several long-standing geographic observations. The incidence of MS and other autoimmune diseases—in which a person's immune system attacks parts of his or her own body—tend to be rare near the equator, where

ultraviolet light from the sun is intense and people produce abundant vitamin D.

For 2 decades, scientists have known that certain immune cells in the blood possess receptors for 1,25-D, the active form of vitamin D. To probe why, Margherita T. Cantorna of Pennsylvania State University in University Park and her colleagues incubated white blood cells with 1,25-D. The team found that the hormone inactivates a type of immune cell called a killer T lymphocyte. These are the cells that launch immune attacks against material invading the body, as well as native cells that have become infected or malignant. Killer T lymphocytes also drive autoimmune diseases.

Over the years, Cantorna's team has shown in animal models of MS, lupus, inflammatory bowel disease, and type 1 diabetes that autoimmune symptoms diminish or disappear after the animal receives either 1,25-D or chemical analogs of it. The group has even shown, in a mouse study, that such drugs can prevent rejection of a transplanted heart.

Cantorna and others have turned to 1,25-D analogs for potential therapeutic applications of vitamin D because excessive amounts of 1,25-D can raise blood-calcium concentrations to toxic levels, which can lead to kidney stones and heart disease.

The analogs that drug companies have devised mimic many of the vitamin's effects on cells but produce less of an increase in blood calcium. Cantorna explains that her animal studies have benefited from the analogs because the 1,25-D doses needed to have an anti-autoimmune effect "were pushing the envelope of what's safe." Companies are now beginning trials with such drugs in patients with autoimmune diseases.

Recently, Cantorna has focused on the mechanism of vitamin D's immune benefits. Her findings indicate that the vitamin's availability during T cell development influences how the mature cells operate. Vitamin D deficiency leads the cells to produce agents that are more reactive to other cells than are those produced when the killer T cells grow up with abundant vitamin D. Cantorna suspects that once full-blown autoimmune disease appears, "you've already lost your window of opportunity to change the kind of T cells that develop."

The immune reaction known as inflammation can also be a leading player in gum disease and tooth loss (SN: 2/24/01, p. 116: Available to subscribers at http://www.sciencenews.org/articles/20010224/fob2.asp). Low blood concentrations of vitamin D were linked to gum disease in a study of 11,200 men and women who had taken part in the federally sponsored National Health and Nutrition Examination Survey, Thomas Dietrich of Boston University's dental school and his colleagues report.

The rate of loss in tooth-gum attachment was 25 percent higher among those participants with the least vitamin D compared to those with the most vitamin. Since poor attachment correlated with low vitamin D even when bone density was taken into account, the investigators say that the observed effect probably stemmed from the vitamin's effect on immunity. They conclude in the July 1 *American Journal of Clinical Nutrition* that vitamin D "may be important for

preventing tooth loss."

Double trouble

Like autoimmune diseases, several cancers—though not skin cancer—become less common in populations the closer they are to the equator. Recent research suggests that vitamin D underlies that geographic pattern, says JoEllen Welsh of the University of Notre Dame (Ind.). In the July 2003 *Journal of Nutrition*, she and her colleagues reviewed laboratory evidence that the vitamin signals colon, breast, and prostate cells to differentiate into mature forms, stop growing, and eventually succumb to programmed cell death. Cancer cells, in contrast, remain immature, rapidly divide, and are immortal. Says Welsh, "We've shown that if you give [a chemical analog of 1,25-D] to an animal that already has a mammary tumor, that tumor will regress." Other researchers, she notes, have used 1,25-D analogs to inhibit the spread of cancer or the growth of blood vessels that feed new tumors in laboratory animals.

Feldman's group has shown that giving men 1,25-D analogs for 2 years can reduce the buildup in blood of a protein marker of cancer—prostate-specific antigen (PSA). The result suggests that the treatment slowed prostate cancer growth, Feldman says. Several human trials are now testing higher doses of the drugs against prostate cancer and a precancerous condition known as benign prostatic hyperplasia.

Scientists are also investigating whether vitamin D can prevent cancer. Welsh and her colleagues are giving lab animals large doses of vitamin D, rather than 1,25-D or an analog. Whereas 1,25-D is toxic at high does, vitamin D is less so. It's converted to 1,25-D only in specific tissues in response to a signal. The kidneys make most of the 1,25-D and put it into circulation throughout the body. Recently, scientists have discovered that cells of the colon, breast, and prostate can also make this substance for local use. In that case, there's no risk of a toxic systemic effect, such as calcium overload in the blood.

Vitamin D may play a role in the prevention of diabetes as well as of cancer. Many studies have linked vitamin D deficiency to an increased risk of type 2 diabetes, which used to be called adult-onset diabetes. However, says Ken C. Chiu of the University of California, Los Angeles School of Medicine, no one knew what aspect of the disease the vitamin might be acting on. So, his team recently recruited 126 healthy adults and correlated their blood concentrations of vitamin D with their production of and response to insulin.

Both these insulin parameters were low, sometimes falling below the normal range, among people with low blood concentrations of vitamin D, the researchers reported in the May 1 *American Journal of Clinical Nutrition*. Vitamin D deficiency "is a double jeopardy for type 2 diabetes," concludes Chiu. He says he now worries that for people on the cusp of developing the disease, vitamin deficiency might tip the balance.

The rub

Today, during much or all of the year, a large share of the U.S. population doesn't even come close to achieving 200 to 600 IU of vitamin D daily. That's the minimum vitamin D intake recommended in 1997 by the National

Academies' Food and Nutrition Board, which sets guidelines for vitamins. However, most recent research on vitamin D suggests that many of its health-promoting actions may require far higher doses.

Indeed, Heaney suspects that such high thresholds for vitamin D sufficiency may explain why many of the vitamin's benefits outside bones escaped notice for so long.

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