

Vitamin D: New D-fence against cardiovascular disease?

Vitamin D is critically important in a wide range of physiological processes, and vitamin D deficiency may play a role in a number of diseases, including cancer and autoimmune diseases.

ABSTRACT: The benefits of vitamin D are well established for skeletal health, but its effects on other organ systems are less clear. Recent observational data suggest that vitamin D may promote cardiovascular health. Individuals with high serum 25(OH)D are less likely to suffer from hypertension, hyperlipidemia, diabetes, angina pectoris, stroke, and myocardial infarction compared with those with low serum 25(OH)D. Individuals with high intake of vitamin D are less likely to suffer from diabetes, myocardial infarction, and stroke. Large-scale randomized controlled trials are underway to further investigate these associations, but current evidence remains insufficient to draw any firm conclusions. In the meantime, a vitamin D intake of 600 IU per day is proven to be safe and effective at promoting bone health, and may provide an accessory benefit of improved cardiovascular health.

A 60-year-old man with diabetes and high blood pressure comes to your office and asks if he should be taking a daily vitamin D supplement in addition to his other medications, and if so, how much? What should you advise this patient? Your recommendation will be based on the knowledge we have about vitamin D, as well as the lack of evidence we have for benefits beyond bone health.

Historically, vitamin D has been known as a key player in calcium metabolism and osteoporosis prevention. It comes in two main forms: cholecalciferol (vitamin D₃) and ergocalciferol (vitamin D₂), both of which are precursors to the biologically active hormone calcitriol, also called 1,25-dihydroxycholecalciferol (1,25(OH)D). Cholecalciferol is synthesized in the skin in a sunlight-dependent reaction and can also be obtained by eating select animal-based foods. Ergocalciferol is typically obtained from plant-based sources. Both forms are widely available as supplements and are also used to fortify orange juice, cereal, and milk.¹

It is now clear that vitamin D is critically important in a wide range of

physiological processes, and that vitamin D deficiency may play a role in a number of diseases, including certain types of cancer and various chronic inflammatory and autoimmune diseases.^{2,3} More recently, compelling evidence has emerged regarding an association between low vitamin D, measured by serum levels of 25-hydroxyvitamin D (25(OH)D), and cardiovascular disease (CVD). This evidence suggests low vitamin D is associated with several important CVD risk factors, including hypertension, an unfavorable blood lipid profile, and diabetes.

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Institute of Medicine current recommendations for vitamin D

In November 2010, the Institute of Medicine (IOM) provided dietary reference intakes (DRIs) for vitamin D ranging from 400 IU/day for infants to 800 IU/day for the elderly. The recommendations were made solely on the basis of bone health. Vitamin D is critical to bone health largely because of its important role in enhancing calcium absorption, and both calcium and vitamin D are needed in sufficient amounts to achieve optimal bone health. Other proposed health benefits of vitamin D are not dependent on calcium, but according to the IOM there is still insufficient and inconclusive evidence to generate DRIs for vitamin D based on nonskeletal health outcomes such as CVD.⁴

The recommended dietary allowances (RDAs) for vitamin D intake shown in the **Table** are designed to achieve a target serum 25(OH)D level of 50 nmol/L or greater in 97.5% of the population. Serum 25(OH)D levels below 50 nmol/L are deemed to be inadequate for bone health.⁴

The tolerable upper intake levels (ULs) for vitamin D are also shown in the **Table**. The tolerable upper intake levels for a nutrient are defined by the IOM as the highest average daily nutrient intake level that is likely to pose no risk of adverse health to almost all individuals in the general population. For vitamin D, acute toxicity becomes a concern at consumption above 10 000 IU/day. Furthermore, a few studies have shown an association between intakes above 4000 IU/day and increased risk of all-cause mortality, cancer, and cardiovascular disease. Such data raise the possibility that vitamin D has a U-shaped relationship with cardiovascular disease.⁴

Table. Current recommended dietary allowances for vitamin D.

| Life stage | Recommended dietary allowance per day | Tolerable upper intake level per day |
|-----------------------|---------------------------------------|--------------------------------------|
| 0–6 months | 400 IU* | 1000 IU |
| 6–12 months | 400 IU* | 1500 IU |
| 1–3 years | 600 IU | 2500 IU |
| 4–8 years | 600 IU | 3000 IU |
| 9–70 years | 600 IU | 4000 IU |
| Pregnant or lactating | 600 IU | 4000 IU |
| > 70 years | 800 IU | 4000 IU |

*The listed RDA values for infants from 0 to 12 months are actually adequate intake values, based on lack of sufficient evidence to generate RDA values.

Low vitamin D and hypertension

Analysis of National Health and Nutrition Examination Survey data from 1988 to 1994 and 2001 to 2006 reveals that low serum 25(OH)D is associated with increased systolic blood pressure. Compared with individuals in the highest of seven quantiles of serum 25(OH)D (> 87.5 nmol/L), those in the lowest quantile (< 25 nmol/L) had a higher average systolic blood pressure by 3.3 mm Hg (n = 27 153, $P < .0001$).⁵

A 2011 meta-analysis of 17 observational studies (pooled N = 78 038), showed a decreased prevalence of hypertension (OR 0.84; 95% CI, 0.78–0.90) for each 40 nmol/L increase in serum 25(OH)D (approximately 2 SDs).⁶

Vitamin D has been shown to inhibit transcription of the gene for renin, which may partly explain the BP-lowering effect observed in the above-mentioned epidemiological studies.⁷

Low vitamin D and higher triglycerides/lower HDL

National Health and Nutrition Examination Survey data from 1988 to 1994 show that low serum 25(OH)D is asso-

ciated with high triglycerides, by a mechanism that is not yet clear. Compared with individuals in the highest quartile of serum 25(OH)D (> 92.5 nmol/L), those in the lowest quartile (< 52.5 nmol/L) were more likely (OR 1.47, $P < .001$) to have a triglyceride level above 1.71 mmol/L (n = 15 088).⁸

National Health and Nutrition Examination Survey data from 2001 to 2006 show an association between low serum 25(OH)D and low HDL cholesterol, though again, no clear mechanism has been elucidated. Individuals in the lowest quintile of serum 25(OH)D (< 35 nmol/L) showed HDL cholesterol levels 0.15 mmol/L lower than those in the highest quintile (> 74.0 nmol/L) (n = 3958, $P < .001$).⁹

Serum 25(OH)D was not significantly associated with LDL cholesterol during either National Health and Nutrition Examination Survey study period.^{8,9}

Low vitamin D and diabetes

National Health and Nutrition Examination Survey data from 1988 to 1994 show an association between low serum 25(OH)D and higher fasting blood glucose levels. Compared with individuals in the highest quartile of

serum 25(OH)D (>92.5 nmol/L), those in the lowest quartile (<53.75 nmol/L) were more likely (OR 1.98, $P < .01$) to have a fasting blood glucose greater than 7 mmol/L ($n = 15\,088$).⁸

National Health and Nutrition Examination Survey data from 2001 to 2006 show an association between low serum 25(OH)D and elevated glycosylated hemoglobin (HbA1c) levels. Compared with individuals in the

showed an 18.6% improvement in insulin secretion in pancreatic beta cells, whereas subjects who received a placebo ($n = 46$) showed a 10.4% reduction in insulin secretion ($P = .046$ for the difference between groups). A possible explanation for the reduced insulin secretion in the control group is that members of this group who were regularly taking supplements containing vitamin D prior to the study

ed arterial stiffness, as determined by flow-mediated dilation and several other measures of arterial and endothelial function.¹³ Evidence from animal models shows that 1,25(OH)D is an important suppressor of inflammation via inhibition of plasminogen activator inhibitor, another marker of risk for CVD.¹⁴ An in vitro study on human macrophages showed that 1,25(OH)D suppresses foam cell formation, preventing macrophage uptake of LDL cholesterol.¹⁵

Vitamin D has been shown to inhibit transcription of the gene for renin, which may partly explain the BP-lowering effect observed in epidemiological studies.

highest quintile of serum 25(OH)D (>74.0 nmol/L), those in the lowest quintile (<35.0 nmol/L) had an increased Hb1Ac by an average of 0.19% ($n = 3958$, $P < .001$).⁹

Higher self-reported vitamin D intake has been associated with a reduced risk of type 2 diabetes. A 2011 meta-analysis of four observational studies ($N = 153\,641$) showed that individuals who consumed more than 500 IU vitamin D per day showed a reduced relative risk (RR) of 0.87 (95% CI, 0.76–0.99) of developing newly diagnosed type 2 diabetes compared with those who consumed less than 200 IU per day.¹⁰

A recent randomized controlled trial (CaDDM) showed that subjects who received 16 weeks of 2000 IU/day vitamin D supplementation ($n = 45$)

period were deprived of their normal vitamin D intake during the 16-week study. Participants were only required to stop taking supplements containing vitamin D 2 weeks prior to the study.¹¹

Vitamin D and other CVD risk factors

Higher vitamin D levels have also been linked to improved vascular endothelial health, reduced inflammation, and reduced foam cell formation, all of which play a role in CVD. One study showed that vitamin D supplementation significantly improved vascular function as measured by flow-mediated dilation in overweight adults;¹² this is supported by another study showing that low serum 25(OH)D was associated with both reduced vascular function and increas-

Vitamin D and cardiovascular disease

A study looking at National Health and Nutrition Examination Survey data from 1988 to 1994 ($n = 16\,603$) showed that individuals with low serum 25(OH)D (<50 nmol/L) have an increased prevalence (OR 1.20, $P = .03$) of angina pectoris, myocardial infarction, or stroke compared to those with higher levels (≥ 50 nmol/L). The study corrected for age, gender, race/ethnicity, season of measurement, physical activity, BMI, smoking status, hypertension, diabetes, elevated LDL cholesterol, hypertriglyceridemia, low HDL cholesterol, chronic kidney disease, and vitamin D use.¹⁶

Low vitamin D intake has also been associated with increased CVD. A recent study evaluated data from the Health Professionals Follow-Up Study of 1986 to 2006 ($N = 44\,592$) and found a significantly reduced incidence (RR 0.84; 95% CI, 0.72–0.97) of myocardial infarction and stroke in men with high vitamin D intake (≥ 600 IU/day) compared to men with low intake (<100 IU/day). The same paper evaluated data from the Nurses' Health Study of 1984 to 2006 ($N = 74\,272$) but found no such association in women (RR 1.02; 95% CI, 0.89–1.17).¹⁷

Conversely, a 2010 meta-analysis of 16 observational studies with CVD as a prespecified outcome (pooled

N = 64 722) showed that men and women with the highest serum 25(OH)D category in each study had a decreased prevalence (OR 0.67; 95% CI, 0.55–0.81) of myocardial infarction, stroke, ischemic heart disease, and peripheral vascular disease compared with those in the lowest serum 25(OH)D category.¹⁸

Low vitamin D status in many Canadians

Although vitamin D can be obtained from dietary sources such as fortified dairy products or fish oil, it is normally synthesized by the skin in adequate amounts upon exposure to sunlight. Ultraviolet radiation (UVB) converts a cholesterol precursor in the skin, 7-dehydrocholesterol, to vitamin D precursors that are then processed by the liver and kidneys to active vitamin D. However, in individuals with dark skin pigment and in individuals who receive minimal sun exposure, the amount of vitamin D produced is reduced, increasing the importance of dietary vitamin D.

A recently published study analyzing data from the Canadian Health Measures Survey of 2007 to 2009 reveals that many Canadians do not have adequate vitamin D levels. Even during the summer months (April to October), nearly one-quarter of Canadians have a serum 25(OH)D below the recommended level of 50 nmol/L. During winter months (November to March) that proportion increases to nearly one-third of the population.¹⁹

The fact that many Canadians do not have adequate vitamin D levels could be attributed to an inadequate diet. According to data from the Canadian Community Health Survey in 2004, only 33% of adults age 19 and over have a usual intake of dietary vitamin D (from food sources only) at or above the recommended intake level. This suggests that the majority

of Canadian adults should be taking a daily vitamin D supplement, either independently or in the form of a multivitamin, to improve their total daily intake.²⁰ According to a phone survey conducted in 2008, 60% of British Columbians reported having used a supplement containing vitamin D at some point in the past month.²¹ Similar data on supplement use are not available for other provinces.

and effect for *any* amount of vitamin D intake and improved cardiovascular health.

Randomized controlled trials are now needed to evaluate the potential benefits of vitamin D intake (at various doses) on cardiovascular disease, while keeping a close eye on any potential harmful effects. One such large-scale, long-term trial (VITAL) funded by the National Institutes of

Observational and epidemiological studies from the past decade collectively show a strong association between low serum 25(OH)D and the prevalence of CVD and its risk factors.

Conclusions

Vitamin D therapy could play a significant role in the prevention and treatment of CVD. Observational and epidemiological studies from the past decade collectively show a strong association between low serum 25(OH)D and the prevalence of CVD and its risk factors. The meta-analyses reviewed in this article uniformly suggest a potential benefit for cardiovascular disease when serum 25(OH)D levels are as high as 80 or 90 nmol/L, a level that could be achieved with a daily vitamin D intake of 2000 IU, an amount well below the tolerable upper intake level of 4000 IU.²² However, for most of these positive associations a clear mechanism of action has yet to be identified, and the current level of evidence is insufficient to prove cause

Health is currently in its early stages. The study will randomly assign 20 000 healthy older men and women to receive daily doses of either 2000 IU of vitamin D₃ or a placebo for 5 years, and will look at prespecified outcomes of cancer, heart disease, and stroke.²³ Preliminary results of VITAL will not be available until at least 2016. Until then, clinicians should be cautious in recommending vitamin D to their patients for anything other than bone health.

Returning to that 60-year-old patient with diabetes and high blood pressure, the evidence currently available supports advising him to supplement his diet with the RDA of 600 IU of vitamin D. In addition the patient should be informed that this amount of vitamin D has been proven to promote

bone health, and that although vitamin D may have a positive effect on diabetes and blood pressure, this remains unproven. The patient should also be warned not to exceed the tolerable upper intake level of 4000 IU of vitamin D per day, as such amounts have been linked with increased all-cause mortality and may do more harm than good.

Competing interests

Dr Ignaszewski has received fees for speaking for Servier Canada and reimbursement for attending a European Society of Cardiology meeting from Boehringer Ingelheim.

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