

## Vitamin D and Diabetes

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Renewed interest in vitamin D, the so-called “sunshine vitamin,” has occurred recently because it has been linked to everything from cancer and heart disease to diabetes.<sup>1</sup> Research studies continue to pour into the literature stating that vitamin D is a superstar when it comes to health. However, most of the research is based on observational, epidemiological studies, which are important for generating hypotheses but do not prove causality.

A PubMed search in 2011 using the term “vitamin D” and selecting articles published in the past 2 years resulted in more than 2,864 hits. The following diseases and conditions have been researched to assess their relationship with vitamin D status: osteomalacia/osteoporosis,<sup>2–5</sup> muscle function and falls,<sup>6–8</sup> cancer,<sup>9–14</sup> multiple sclerosis,<sup>15</sup> hypertension,<sup>16</sup> type 1 diabetes,<sup>17</sup> rheumatoid arthritis,<sup>18</sup> tuberculosis,<sup>19,20</sup> mental health,<sup>21</sup> cardiovascular events,<sup>22,23</sup> infection,<sup>24,25</sup> seasonal affective disorder,<sup>26</sup> obesity,<sup>27</sup> aging,<sup>28</sup> and overall mortality.<sup>23</sup>

The challenge for health care providers and nutrition researchers is to determine whether vitamin D deficiency actually causes or increases the incidence of certain diseases or whether, instead, low levels of vitamin D are simply coincidental given that the majority of the general population, regardless of disease, is likely to have insufficient levels of vitamin D. In other words, do people who develop disease states just happen to be deficient in vitamin D, or do low levels of vitamin D cause the disease? Will supplementation with vitamin D prevent diseases, and can

it be used to treat diseases such as diabetes?

The purpose of this article is to summarize the latest information related to diabetes and vitamin D. For readers who desire further information, Holick<sup>29</sup> has written extensively about the high prevalence of vitamin D deficiency and its implications for health. There is also an excellent recent review of vitamin D insufficiency by Thatcher and Clarke.<sup>1</sup>

### Clinical Understanding of Vitamin D

There are two main forms of vitamin D: ergocalciferol (vitamin D<sub>2</sub>) and cholecalciferol (vitamin D<sub>3</sub>). Vitamin D<sub>2</sub> is synthesized by plants (mainly mushrooms and yeast), whereas vitamin D<sub>3</sub> is synthesized in skin when it is exposed to ultraviolet B rays from sunlight. Vitamin D<sub>3</sub> is also found in a few foods such as fatty fish.<sup>30</sup>

Unfortunately, it is very difficult to get enough vitamin D from food sources alone. Both vitamin D<sub>2</sub> and vitamin D<sub>3</sub> can be made synthetically and are used to fortify foods such as milk products, margarine, and soy milk and to make dietary supplements. The synthetic form of vitamin D<sub>3</sub> is derived from animal sources and is currently the most common form of vitamin D used in supplements and fortified foods.<sup>31</sup>

The dietary forms of vitamin D are absorbed in the small intestine with dietary fats and other fat-soluble vitamins, whereas vitamin D<sub>3</sub> enters circulation after it is synthesized nonenzymatically in the skin during exposure to the ultraviolet rays in sunlight. Neither vitamin D<sub>2</sub> nor vitamin D<sub>3</sub> have any biological functions in the body until they

go through a two-step process of metabolism.<sup>2</sup> The metabolism of the various forms of vitamin D requires conversion in the liver and kidney, and the active form, 1,25-dihydroxyvitamin D (calcitriol), needs to bind to vitamin D receptors (VDRs) before biological actions occur.<sup>32,33</sup>

Thus, diabetic patients with liver or kidney problems are at high risk of deficiency, as are patients with gastrointestinal disorders such as celiac disease, pancreatitis, low bile levels, or sprue.<sup>34</sup>

In the past, the major source of vitamin D for humans was exposure to sunlight. One possible cause of the current widespread vitamin D deficiency is the lack of sunlight exposure. Another possible cause is a lack of dietary sources of vitamin D.<sup>32</sup>

Since the industrial revolution, very few people get much sun exposure while working. Other barriers to sunshine exposure include fear of skin cancer, which has led to an increased use of sunscreen, hats, and other sun barriers. For some people, religious beliefs require that their skin be covered. Environmental factors such as pollution and fewer hours of sun exposure during the winter (especially in latitudes north of ~ 37°) also decrease vitamin D synthesis from sunlight exposure.<sup>35</sup> Additionally, aging skin and skin of darker color require longer exposure to sunlight to initiate vitamin D synthesis.<sup>34</sup>

It has been suggested that ~ 5–30 minutes of sun exposure between 10:00 a.m. and 3:00 p.m. at least twice per week on the skin of the face, arms, back, or legs (without sunscreen) is usually adequate for vitamin D synthesis.<sup>2,36</sup> Skin exposed to sunshine indoors, as through a glass window, will not produce vitamin D.<sup>37</sup>

The most accurate way to determine vitamin D status is to measure 25-hydroxy vitamin D [(25(OH)D)]. The optimal range is 25–80 ng/ml. However, normal value ranges may vary slightly among different laboratories.<sup>38</sup> Table 1 lists categories of vitamin D status based on 25(OH)D measurement.

The Food and Nutrition Board of the Institute of Medicine (IOM)

**Table 1. Categorization of Vitamin D Levels<sup>38</sup>**

< 10 ng/ml	Severe deficiency
10–24 ng/ml	Mild to moderate deficiency
25–80 ng/ml	Optimal levels
> 80 ng/ml	Toxicity possible

recently updated the Dietary Reference Intake (DRI) for vitamin D.<sup>39</sup> The IOM recommends 600 IU/day of vitamin D for individuals aged 9–70 years and 800 IU/day for those > 70 years of age.<sup>40</sup> However, others recommend that supplementation with vitamin D<sub>3</sub> should be prescribed with the objective of achieving a serum 25(OH)D level of at least 40 ng/ml and possibly even 60 ng/ml.<sup>40</sup> Table 2 lists the new DRIs for vitamin D.

**Treatment of Vitamin D Deficiency**

The two forms of vitamin D supplements are D<sub>2</sub> (ergocalciferol) and D<sub>3</sub> (cholecalciferol). Both increase vitamin D in the blood. Vitamin D supplements are readily available, inexpensive, easy to administer, and safe. At high doses, vitamin D<sub>2</sub> may be less potent than vitamin D<sub>3</sub>.<sup>37</sup>

The safe upper limit for vitamin D is 1,000–1,500 IU/day for infants, 2,500–3,000 IU/day for children aged 1–8 years, and 4,000 IU/day for children ≥ 9 years of age, adults, and pregnant and lactating teens and women.<sup>39</sup>

Although levels of supplementation used in practice vary among practitioners, recommendations do exist within the literature. One group<sup>41</sup> recommends the following for vitamin D repletion: 1,000 IU/day of vitamin D<sub>3</sub> if 25(OH)D is 30–40 ng/ml, 2,000 IU/day of vitamin D<sub>3</sub> if 25(OH)D is 20–30 ng/ml, and, for adults with serum levels < 20 ng/ml, prescribe 50,000 IU of vitamin D<sub>2</sub> once to three times per week for 4 weeks followed by 3,000 IU/day until serum 25(OH)D levels are > 30 ng/ml. Then, recheck serum 25(OH)D levels 3–6 months later,

**Table 2. Current DRI Recommendations for Vitamin D<sup>39</sup>**

The following are recommendations for vitamin D in the DRIs developed by the Food and Nutrition Board at the Institute of Medicine. DRI is the general term for a set of reference values used to plan and assess the nutrient intake of healthy people. These values, which vary by age and sex, include:

- Recommended Dietary Allowance (RDA): average daily level of intake sufficient to meet the nutrient requirements of nearly all (97–98%) healthy people
- Adequate Intake (AI): established when evidence is insufficient to develop an RDA and is set at a level assumed to ensure nutritional adequacy

**DRIs for vitamin D**

**Infants**

- 0–6 months: AI: 400 IU (10 µg/day)
- 7–12 months: AI: 400 IU (5 µg/day)

**Children**

- 1– 3 years: 600 IU (15 µg/day)
- 4–8 years: 600 IU (15 µg/day)

**Older Children and Adults**

- 9–70 years: 600 IU (15 µg/day)
- Adults > 70 years: 800 IU (20 µg/day)
- Pregnancy and lactation: 600 IU (15 µg/day)

and continue treating until serum levels are > 40 ng/ml.

Some experts have found that between 2,000 and 4,000 IU/day of vitamin D<sub>3</sub> is necessary to reduce the risks of cancer and autoimmune disease and therefore recommend these higher doses for patients with these specific disease states.<sup>42</sup> Experts also recommend supplementing infants and children with at least 400 IU/day of vitamin D<sub>3</sub>, especially infants who are breastfed.<sup>34</sup>

Controversy often follows recommendations related to micronutrients and disease states, and the case of vitamin D is no different. Experts from the IOM, which is an arm of the National Academy of Sciences, caution that more vitamin D is not necessarily better for all patients. The IOM concluded in its 2010 report<sup>39</sup> that the evidence for a benefit of vitamin D in bone health is compelling, but that for other conditions such as cancer and cardiovascular disease, the evidence is inconclusive and insufficient to drive specific nutritional requirements for vitamin D intake. The report also says that cut points for testing for vitamin D levels in blood are not grounded in strong scientific evidence and that these cut points may be leading to an overestimation of the prevalence of vitamin D deficiency.<sup>39</sup>

The variance in recommendations and clinical practice has the potential to confuse patients and health care providers, but it demonstrates that there may be a wide range of dosing recommendations for vitamin D depending on a specific patient's disease-state status and level of deficiency. It is reassuring to know that vitamin D supplementation is relatively safe and that cases of toxicity are rare and have been observed only when patients are taking > 40,000 IU/day.<sup>43</sup>

The IOM recommendations hopefully will not be misinterpreted and cause people to stop taking supplements if their 25(OH)D levels are low. In addition, as was noted in the IOM report, additional research is needed regarding the role of vitamin D in various disease states, including diabetes.

### Vitamin D and Diabetes

Vitamin D deficiency and diabetes have one major trait in common: both are pandemic. The International Diabetes Federation estimates the number of people with diabetes worldwide to be nearly 285 million, or 7% of the world's population.<sup>44</sup> This number is expected to exceed 435 million by 2030.<sup>44</sup> In the United States, an estimated 79 million people have pre-diabetes.<sup>45</sup>

### Mechanisms of action

There is growing evidence that vitamin D deficiency could be a contributing factor in the development of both type 1 and type 2 diabetes. First, the  $\beta$ -cell in the pancreas that secretes insulin has been shown to contain VDRs as well as the 1 alpha hydroxylase enzyme.<sup>46</sup> Evidence indicates that vitamin D treatment improves glucose tolerance and insulin resistance.<sup>47,48</sup> Vitamin D deficiency leads to reduced insulin secretion. Supplementation with vitamin D has been shown to restore insulin secretion in animals.<sup>49</sup> Researchers have also found an indirect effect on insulin secretion, potentially by a calcium effect on insulin secretion. Vitamin D contributes to normalization of extracellular calcium, ensuring normal calcium flux through cell membranes; therefore, low vitamin D may diminish calcium's ability to affect insulin secretion.<sup>50</sup> Other potential mechanisms associated with vitamin D and diabetes include improving insulin action by stimulating expression of the insulin receptor, enhancing insulin responsiveness for glucose transport, having an indirect effect on insulin action potentially via a calcium effect on insulin secretion, and improving systemic inflammation by a direct effect on cytokines.<sup>50</sup>

### Vitamin D and type 2 diabetes

After conducting a meta-analysis and review of the impact of vitamin D and calcium on glycemic control in patients with type 2 diabetes, Pittas et al.<sup>50</sup> concluded that insufficient vitamin D and calcium appears to hinder glycemic control and that supplementing both nutrients may be necessary to optimize glucose metabolism. An observational study

from the Nurses Health Study<sup>51</sup> that included 83,779 women > 20 years of age found an increased risk of type 2 diabetes in those with low vitamin D status. A combined daily intake of > 800 IU of vitamin D and 1,000 mg of calcium reduced the risk of type 2 diabetes by 33%. The National Health and Nutrition Examination Survey (NHANES) III study between 1988 and 1994<sup>52</sup> demonstrated that there is a strong inverse association between low levels of 25(OH)D and diabetes prevalence. Low vitamin D levels have also been shown to be predictive of the future development of type 2 diabetes.<sup>53</sup> One study<sup>54</sup> showed that increasing vitamin D serum levels to normal led to a 55% relative reduction in the risk of developing type 2 diabetes. As with most disease states and vitamin D, prospective studies related to vitamin D supplementation and diabetes are rare and limited. Prospective trials of vitamin D and diabetes to date were either too small or used inadequate amounts of vitamin D.<sup>55</sup>

Kayaniyil et al.<sup>56</sup> performed a linear regression analysis of 712 subjects after evaluating serum 25(OH)D levels and assessing insulin sensitivity by means of the homeostasis model of insulin resistance. Their results indicated that vitamin D was significantly correlated to insulin resistance and  $\beta$ -cell function in their multiethnic sample. The researchers concluded that low vitamin D levels may play a significant role in the pathogenesis of type 2 diabetes.

The NHANES group (2003–2006) evaluated 9,773 U.S. adults > 18 years of age and showed a mechanistic link between serum vitamin D levels, glucose homeostasis, and the evolution of diabetes.<sup>57</sup> Based on their own study, Kositsawat et al.<sup>58</sup> concluded that patients with elevated A1C levels should be evaluated for vitamin D insufficiency.

### Vitamin D and type 1 diabetes

Observational studies also suggest that low vitamin D status may be associated with an increased risk of type 1 diabetes. For example, there is a greater incidence of type 1 diabetes related to geographic variation, with locations at higher latitudes having more type 1 diabetes. This may be

the result of less sunshine and, therefore, lower levels of vitamin D.<sup>59</sup>

Hyponen et al.<sup>60</sup> conducted a cohort study in northern Finland. They collected data during 1 year on 10,821 children regarding vitamin D supplementation dose and presence of suspected rickets as it related to the development of type 1 diabetes. Their findings were both significant and astounding; children who took 2,000 IU of vitamin D daily were 80% less likely to develop type 1 diabetes. This suggests that it may be crucial for all children to take vitamin D supplementation during their first year of life to help avoid the development of type 1 diabetes.

Another vitamin D study conducted by Zipitis et al.<sup>61</sup> demonstrated that vitamin D supplementation in early childhood decreased the risk of developing type 1 diabetes by 29% compared to children who were not given vitamin D supplements. In addition, the researchers found evidence suggestive of a dose-response effect.

Because destruction of  $\beta$ -cells usually begins in infancy or early childhood and continues until type 1 diabetes is diagnosed, studies such as these are intriguing in terms of the utility of vitamin D in people with type 1 diabetes. It is hoped that starting vitamin D supplementation soon after birth may be a protective strategy against the development of type 1 diabetes.<sup>34</sup>

Another area of interest is vitamin D status during pregnancy and lactation and whether a pregnant woman's vitamin D status plays a role in the development of diabetes in her child. Gregory et al.<sup>62</sup> suggest that pregnant women and nursing mothers should take supplements to make sure their vitamin D serum levels are optimal. This group reasoned that, because vitamin D is a powerful modulator of the immune system and helps regulate cell proliferation and differentiation, it seems clear that vitamin D could play a role in preventing type 1 diabetes. Their research showed that adequate vitamin D status in mothers did have an impact on reducing the development of type 1 diabetes in their children.

However, studies related to the precise dose and duration of vitamin D supplementation in infants and children are lacking. Currently, 400 IU of vitamin D<sub>3</sub> is recommended for supplementation in all infants until enough formula, milk, or other food sources are ingested to sufficiently provide 400 IU/day.<sup>63</sup> Although it seems prudent and reasonable to supplement infants, children, and adolescents with vitamin D to prevent deficiency, there is inconsistency in the recommended vitamin D dose.

Currently, evidence supports that maintaining adequate vitamin D status during pregnancy, nursing, infancy, and childhood may help prevent type 1 diabetes. However, it is still unknown whether the genetics of type 1 diabetes place individuals at risk for vitamin D deficiency or whether vitamin D deficiency places individuals at risk for type 1 diabetes.

Also lacking are studies to support that vitamin D would improve the treatment of type 1 diabetes after diagnosis. Only a few intervention studies have examined the impact of vitamin D supplementation on reversing type 1 diabetes, and they have not been successful.<sup>62</sup>

### Summary and Conclusion

Although the role of vitamin D in helping to regulate blood glucose remains poorly understood, vitamin D status appears to play a role in the development and treatment of diabetes. It is possible that optimal levels of serum vitamin D may be different for people at risk for developing diabetes, those with diabetes, and those without diabetes. According to Danescu et al.<sup>64</sup>, "both animal and human studies support the notion that adequate vitamin D supplementation may decrease the incidence of type 1 and possibly also of type 2 diabetes mellitus and may improve the metabolic control in the diabetes state. However, the exact mechanisms are not clear and need further investigation."

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