

Symposium: Vitamin D Insufficiency: A Significant Risk Factor in Chronic Diseases and Potential Disease-Specific Biomarkers of Vitamin D Sufficiency

Vitamin D in Type 1 Diabetes Prevention¹

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ABSTRACT Limited data from human observational studies suggest that early supplementation with 10 $\mu\text{g}/\text{d}$ (400 IU/d) or less of vitamin D may not reduce the risk for type 1 diabetes but that doses of 50 $\mu\text{g}/\text{d}$ (2000 IU/d) and higher may have a strong protective effect. Current U.S. recommendations (5–25 $\mu\text{g}/\text{d}$, 200–1000 IU/d) fall in the largely unstudied dose range in between. All infants and children should receive between 5 $\mu\text{g}/\text{d}$ and 25 $\mu\text{g}/\text{d}$ of supplemental vitamin D, particularly if they have limited sun exposure, live in northern areas, are exclusively breastfed, or are dark skinned. Caretakers of infants and children at increased risk of type 1 diabetes might wish to consider supplementation toward the upper end of that range or above. Additional studies are needed that 1) investigate the association between 25-hydroxyvitamin D and autoantibodies predictive of type 1 diabetes in infancy and beyond, 2) test the ability of vitamin D supplement doses between 5 and 50 $\mu\text{g}/\text{d}$ to prevent autoantibodies and/or type 1 diabetes in infancy and beyond, and 3) examine the safety of vitamin D intakes of 25 $\mu\text{g}/\text{d}$ and higher. Also, we need to consider the possible benefits of vitamin D supplementation when deciding whether or not to screen children for type 1 diabetes risk and to add type 1 diabetes to the growing list of outcomes that are considered when vitamin D recommendations are next revised. *J. Nutr.* 135: 323–325, 2005.

KEY WORDS: • type 1 diabetes • autoimmune antibodies • vitamin D infant supplements • 25-hydroxyvitamin D • vitamin D-fortified infant formula • cod-liver oil • and insulin

Type 1 diabetes

Type 1 diabetes results from autoimmune destruction of insulin-producing β cells in the islets of the pancreas. The specific factors that initiate the autoimmune process are not yet well understood, but β cell destruction often begins during infancy and continues over many months or years (1). Peak incidence occurs around puberty, and the disease is usually diagnosed before age 30. By the time type 1 diabetes is diagnosed, about 80% of the β cells have been destroyed (2).

Autoantibodies

Autoantibodies to β cells and their antigens are detectable in the blood long before a person develops type 1 diabetes (2). Although not everyone with detectable autoantibodies goes on to develop the disease, high levels of single autoantibodies and the presence of multiple autoantibodies are highly predictive of future disease, both in relatives of type 1 diabetics and in others (3–5). These autoantibodies provide a way to evaluate risk factors for type 1 diabetes over a shorter period than studies of diabetes incidence would require. For example, a recent European study used the presence of autoantibodies as a surrogate outcome to demonstrate that consumption of gluten-containing foods before the age of 3 months may increase the risk for type 1 diabetes (6).

There is an important genetic influence on type 1 diabetes risk: the lifetime risk for the disease is 6% for people with affected first-degree relatives compared with 0.4% in the general white population (7). However, low concordance among identical twins and the fact that many children with a genetic predisposition to the disease do not develop it suggest that environmental factors are also important (8). It is possible to test newborns for a genetic predisposition to type 1 diabetes, as well as to screen older infants and children for predictive autoantibodies, but there has been a reluctance to do so, in part, because of the absence of preventive treatments (5,9). The public health benefit of screening infants for diabetes risk

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would be more evident if safe and effective preventive treatments were available. The purpose of this discussion is to examine the evidence that supplementing infants with vitamin D might be a safe and effective strategy for preventing type 1 diabetes.

Vitamin D

Vitamin D is produced endogenously when the skin is exposed to sunlight and can be obtained exogenously from foods and supplements. Though influenced by the vitamin D status of the mother (10), breast milk typically contains little vitamin D. Aside from sunlight exposure, the primary sources of vitamin D for infants are infant formula and infant vitamin supplements. Skin production of vitamin D depends on time spent outside, coverage of the skin with clothing and sunscreen, skin color, season of the year, and latitude. In northern areas, including the northern United States, Canada, and most of Europe, little or no vitamin D is produced in the skin during winter months (11). Even in the summer and at lower latitudes, many infants are so thoroughly protected from sun exposure that they produce little endogenous vitamin D. Vitamin D, whether endogenous or exogenous, is converted in the liver to 25-hydroxyvitamin D [25(OH)D],³ the storage form of the vitamin and the best overall indicator of vitamin D status.

Although the importance of vitamin D for preventing rickets and adult bone disease is well established, it is becoming increasingly clear that vitamin D may also be related to other medical conditions. In particular, it appears to be an immunosuppressive agent (12), a role that may explain its protective association with autoimmune conditions, including multiple sclerosis (13) and rheumatoid arthritis (14).

Adequate intakes (AI) of vitamin D were published by the Institute of Medicine in 1997 (15). The AI "represents the intake . . . likely to maintain adequate serum 25(OH)D for individuals . . . unable to obtain sunlight." In infants, the AI was selected based on data suggesting that it would prevent rickets and produce 25(OH)D concentrations similar to those of infants with ample sun exposure. A value of 5 $\mu\text{g}/\text{d}$ (200 IU/d) was selected for infants and children. This is an amount that is unlikely to be consumed by infants who are exclusively breastfed, whereas formula-fed infants would get approximately that amount, depending on the amount of formula consumed (Table 1). U.S. infant supplements, in contrast, provide twice the AI for vitamin D.

Vitamin D and type 1 diabetes

Strong evidence of a vitamin D effect on type 1 diabetes risk comes from experiments in the nonobese diabetic (NOD) mouse. The NOD mouse experiences disease pathogenesis similar to the human, including autoimmune destruction of β cells. When 1,25-dihydroxyvitamin D [1,25(OH)₂D], the active form of the vitamin, was administered to NOD mice in pharmacologic doses, it prevented the development of diabetes (16). More recently, NOD mice raised in a vitamin D deficient state were shown to develop diabetes at an earlier age than nondeficient NOD controls (17).

Several European observational studies in humans have now raised the possibility that providing supplemental vitamin D to infants may prevent the development of type 1 diabetes (18–20). These studies did not include measurements of 25(OH)D and care therefore must be taken in extrapolating

TABLE 1

Typical vitamin D content of infant diets and supplements

Age	Energy	Breast milk only vitamin D	Formula only vitamin D	Supplements vitamin D
	<i>kcal/d</i>		<i>$\mu\text{g}/\text{d}$</i>	
Birth	360	0.6	3.6	10.0
5 mo	630	1.0	6.3	10.0

their results to other populations in which vitamin D concentrations of unsupplemented children may differ. In addition, 2 of the studies were case-control studies that required mothers to recall their children's vitamin D intakes many years earlier, limiting the extent and possibly the quality of the vitamin D intake data.

The first of these studies was a large case-control study conducted in 7 European countries (18). The parents of 820 diabetic children and 2335 population-based controls were interviewed to determine whether or not their children had been given vitamin D supplementation during the first year of life. Specific vitamin D supplement types and doses were not reported. The risk for type 1 diabetes by age 15 was reduced by about a third in the supplemented compared with unsupplemented children (odds ratio 0.67).

Another large case-control study was conducted by Stene et al. (19) in Norway. Parents of 545 diabetic children identified from a national registry and 1668 population-based controls responded to mailed questionnaires, which included questions about their children's intakes of vitamin D supplements and cod-liver oil during the first year of life. Individual vitamin D doses from these products were not assessed, but the manufacturers' recommended doses for the most commonly used brands of both cod-liver oil and other vitamin D supplements would have provided 10 $\mu\text{g}/\text{d}$ (400 IU/d) of vitamin D. Cod-liver oil given to the infants at least 5 times a week was associated with a significant reduction in diabetes risk compared with no supplementation (odds ratio 0.74). However, there was no evidence of a protective effect of other vitamin D supplements whether taken 1 to 4 times per wk (odds ratio 0.99) or 5 or more times per week (odds ratio 0.97). The reason for the different associations of cod-liver oil and other vitamin D with diabetes risk is unclear. The authors suggest that vitamin D in cod-liver oil may be more bioavailable than vitamin D in other forms or that a different component of cod-liver oil, such as marine fatty acids, may explain the risk reduction.

The first prospective study of vitamin D supplementation in infants and type 1 diabetes was published in 2001 by Hyppönen et al. (20). All 12,055 pregnant women who lived in 1 of 2 regions of Northern Finland were enrolled in the study, and 91% of their living children had multiple assessments of vitamin D supplementation during their first year, recorded by medical personnel at health examinations. Incident cases of diabetes over the subsequent 30 y were identified from national databases. Compared with children who were not given vitamin D supplements, the relative risk of developing type 1 diabetes was only 0.12 among children given vitamin D supplements regularly and 0.16 among children given them irregularly. Among infants who were given supplements regularly, diabetes risk was lower at doses of over 50 $\mu\text{g}/\text{d}$ or 2000 IU/d (relative risk 0.14) and exactly 50 $\mu\text{g}/\text{d}$ (relative risk 0.22) compared with doses under 50 $\mu\text{g}/\text{d}$. Thus this large, well-designed, prospective study provides compelling evidence that vitamin D supplementation of 50 $\mu\text{g}/\text{d}$ (2000 IU/d) or more

³ Abbreviations used: 25(OH)D, 25-hydroxyvitamin D; AI, adequate intakes; NOD, nonobese diabetic.

during infancy may reduce the risk for type 1 diabetes, at least in very northern parts of the world where sunlight is severely limited during a greater part of the year.

A possible explanation for the seemingly contradictory findings of the Stene and Hyppönen (19,20) studies is that vitamin D supplements may prevent diabetes only when given in relatively large doses. The approximate doses from the 2 studies and their observed associations with type 1 diabetes are summarized in **Table 2**. Because the actual doses of irregular users in the Hyppönen study are unknown, it is possible that a beneficial effect of vitamin D supplementation becomes apparent only at doses close to 50 $\mu\text{g}/\text{d}$ (2000 IU/d), an intake much higher than that of infants in the Stene study and also much higher than current recommendations.

A tolerable upper intake level was set by the Institute of Medicine in 1997 at 25 $\mu\text{g}/\text{d}$ (1000 IU/d) for infants (0–12 mo) and 50 $\mu\text{g}/\text{d}$ (2000 IU/d) for children (15). The tolerable upper intake level represents the “maximal level of nutrient intake that is unlikely to pose risks of adverse health effects to almost all individuals in the target group.” For infants, it was based on extremely limited data related to growth and hypercalcemia. With respect to hypercalcemia, the committee concluded that “excessive vitamin D intake is probably a risk factor in a few sensitive infants.”

Taken together, the limited data from human observational studies of type 1 diabetes suggest that there may be no preventive effect of early supplementation with 10 $\mu\text{g}/\text{d}$ (400 IU/d) of vitamin D or less, and a strong protective effect with doses of 50 $\mu\text{g}/\text{d}$ (2000 IU/d) and higher. Given that current U.S. recommendations (5–25 $\mu\text{g}/\text{d}$ or 200–1000 IU/d) fall in the largely unstudied dose range, the clinical implications of these findings are difficult to assess.

Implications

From a clinical standpoint, it would seem prudent to ensure that all infants and children receive between 5 $\mu\text{g}/\text{d}$ and 25 $\mu\text{g}/\text{d}$ (200 and 1000 IU/d) of supplemental vitamin D, particularly if they have limited sun exposure, live in a northern area, are exclusively breastfed, or are dark skinned. This level of supplementation might or might not reduce their risk for type 1 diabetes, but it is unlikely to cause any harm and might provide other health benefits. Parents and health care providers of infants and children at increased risk of type 1 diabetes might wish to consider supplementation toward the upper end of that range or above.

From a research standpoint, we need to verify previous findings and to extend them by 1) investigating the association

between 25(OH)D and autoantibodies predictive of type 1 diabetes in infancy and beyond, 2) testing (preferably in randomized, controlled trials) the ability of vitamin D supplement doses between 5 and 50 $\mu\text{g}/\text{d}$ (200 and 2000 IU/d) to prevent autoantibodies and/or type 1 diabetes in infancy and beyond, and 3) further examining the safety of vitamin D intakes of 25 $\mu\text{g}/\text{d}$ (1000 IU/d) and higher.

From a policy standpoint, we need to consider the possible benefits of vitamin D supplementation in the debate over screening for type 1 diabetes risk, and also to add type 1 diabetes to the growing list of outcomes that are considered when vitamin D recommendations are next revised.

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TABLE 2

Vitamin D supplement doses in infancy and the risk of type 1 diabetes

Study and frequency of supplementation	Vitamin D dose (approximate)	Relative risk of type 1 diabetes (vs. no supplement)
	$\mu\text{g}/\text{d}$	
Stene (19), 1–4 d/wk	<6	0.99
Stene (19), 5+ d/wk	6–10	0.97
Hyppönen (20), irregular	1–49	0.16
Hyppönen (20), regular	50	0.12