

screening those populations at risk, including first- and second-degree relatives of patients with celiac disease, patients with type 1 diabetes, patients with immune thyroid or liver disorders, patients with Sjogrens syndrome, patients with Down or Turner syndrome, and patients with selective IgA deficiency.¹⁴ The key to these questions rests in further understanding the pathophysiology of celiac disease. Studies to date have included the “tip of the iceberg,” but further research is needed to identify those patients under the waterline and how to appropriately treat them.

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Can Vitamin D Supplementation in Infancy Prevent Type 1 Diabetes?

Several recent European studies suggested that supplementing infants with vitamin D during their first year might prevent type 1 diabetes. A dose of 50 µg/day was associated with decreased diabetes risk in Finland, but the effectiveness of lower doses was not examined. The recommended dietary intake of vitamin D for U.S. infants is 5 µg/day and the tolerable upper level is 25 µg/day. There is no evidence that intakes between 5 and 25 µg/day would reduce diabetes incidence, but it would seem prudent to ensure that infants reach at least the lower end of this range.

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Vitamin D is produced endogenously when the skin is exposed to sunlight and can be obtained exogenously from foods and supplements. Endogenous vitamin D production depends on the length of time spent outside, clothing and sunscreen, season of the year, and espe-

cially important, latitude. In northern areas including New England, Canada, and Northern Europe, little or no vitamin D is produced in the skin during winter months.¹ This is not simply a result of reduced sunlight exposure, but of the different, less effective angle at which sunlight penetrates the atmosphere in the winter. Thus, although sunlight exposure is the principal source of vitamin D in free-living populations, it may not provide sufficient vitamin D, especially in winter, to prevent disease. Researchers have long known that vitamin D deficiency causes rickets in children and osteomalacia in adults. More recently, less pronounced vitamin D deficits have been associated with increased rates of bone loss and fracture;^{2–4} more limited evidence suggests that they may be associated with such diverse chronic conditions as hypertension,⁵ certain cancers,^{6–8} type 2 diabetes,⁹ and autoimmune disorders, including multiple sclerosis.¹⁰

Because breast milk contains little vitamin D, infants are dependent on sunlight exposure and dietary or supplemental vitamin D to maintain adequate vitamin D stores. Infant formulas are fortified with vitamin D, but most of the other foods that contain vitamin D, notably fortified cows milk, fortified cereals, and some fish, are

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not routinely given to infants. Approximately two hours per week of sunlight exposure to the face is thought to provide infants with adequate vitamin D in some areas,¹¹ but this exposure is unlikely to be sufficient in the winter in northern areas or for infants who are protected entirely from the sun. Thus, breastfed infants who do not receive supplements are likely to have low circulating vitamin D levels for at least part of the year in northern areas.

Type 1 diabetes results from autoimmune destruction of the insulin-producing beta cells of the pancreas, but the specific trigger of this process is unknown. Most cases of type 1 diabetes are diagnosed before age 30, and peak incidence in the United States occurs around age 12. Several European observational studies have now raised the possibility that providing supplemental vitamin D to infants may prevent the development of type 1 diabetes.^{12–14} Prior to these studies, evidence that vitamin D might protect against the disease came primarily from geographic studies that demonstrated a south-to-north increase in disease incidence¹⁵ and from studies in which treatment with the active metabolite of vitamin D, 1,25-dihydroxyvitamin D [1,25(OH)₂D], prevented the development of clinical diabetes in the nonobese diabetic mouse.¹⁶ Increasing evidence suggests that type 1 diabetes may be mediated by Th 1 lymphocytes, a class of cells involved in immune responses characterized by inflammation and cytotoxicity, and it has been suggested that 1,25(OH)₂D treatment may protect against disease by inhibiting the Th 1 pathway.¹⁷

The first study to examine the association of supplemental vitamin D during infancy with type 1 diabetes in humans was published in 1999.¹² It was a large case-control study conducted in seven European countries that ranged in latitude from approximately 42° N to 57° N. For comparison, the latitudes of Miami and Boston, United States, are 25° N and 42° N, respectively. Thus, although blood measurements of vitamin D and metabolites were not made, one would expect circulating vitamin D levels of unsupplemented subjects in this study to be somewhat lower than those of most people in the United States and southern Europe. A total of 820 cases and 2335 population-based controls with similar age distributions participated in the study. Mothers of the subjects were interviewed to determine whether or not their children had been given vitamin D supplementation during the first year of life. The authors reported an adjusted odds ratio of 0.65 (95% confidence interval [CI], 0.52–0.83), suggesting that supplemented infants have only two-thirds the risk of developing type 1 diabetes by age 15 compared with unsupplemented infants. Adjustments were made for duration of breastfeeding, maternal age, birth weight, and study center. No information was provided regarding supplement doses.

The results of a second case-control study, con-

ducted by Stene et al.¹³ in Norway, were published in 2000. Norway is located at approximately latitude 60° N. Parents of 85 diabetic children identified from a national registry and 1071 randomly selected controls responded to mailed questionnaires about mothers' vitamin D intakes during pregnancy and children's intake during the first year of life. In this study, a distinction was made between vitamin D in cod liver oil and vitamin D from multivitamins and other supplements. Cod liver oil taken by mothers during pregnancy was found to be associated with a reduced risk of type 1 diabetes by age 15 in their children. The odds ratio was 0.36 (CI, 0.14–0.90), suggesting a protective effect of exposure to cod liver oil in utero. Cod liver oil given to the infant was associated with a more modest and not statistically significant reduction in risk, with an odds ratio of 0.82 (CI, 0.47–1.42). There was no evidence of a protective effect of other vitamin D supplements taken by either mother or infant. The authors adjusted infant analyses for age at time of data collection, sex, breastfeeding, maternal education, and other supplement use. The reasons for the different associations of cod liver oil and other vitamin D supplements with diabetes are unclear. The authors speculate 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 apparent risk reduction. Although the average vitamin D doses obtained from cod liver oil and other vitamin D supplements were not reported, the authors mention that pregnant women in another Scandinavian study obtained higher vitamin D doses from cod liver oil than from other vitamin D supplements. (Gry Hay et al. Institute for Nutrition Research, University of Oslo, unpublished data.) It is possible that the vitamin D doses from cod liver oil were also higher in the present study, and that similar effects would have been seen for the two sources if comparably high doses had been taken by mothers or infants.

The first prospective study of vitamin D supplementation in infants and type 1 diabetes was published in 2001 by Hyppönen et al.¹⁴ It was a large cohort study conducted in Northern Finland, an area north of latitude 60° N, and among the farthest of all inhabited areas from the equator. All of the 12,055 pregnant women who lived in one of two regions and expected to give birth in 1966 were enrolled in the study, and 91% of their living children had repeated assessments of vitamin D supplementation during their first year. Information about supplement use was obtained from mothers and was classified as <50 µg/day, exactly 50 µg/day (the recommended amount in Finland at the time), or >50 µg/day. Only 84 of the children had been given cod liver oil, and they were included in the highest vitamin D dose category. Incident cases of diabetes during the subsequent 30

years were identified from national databases. Eighty-eight percent of the children were given vitamin D supplements in their first year and most of them got at least 50 $\mu\text{g}/\text{day}$ on a regular basis. The relative risk of developing type 1 diabetes by age 30 among children who were given vitamin D supplements regularly was only 0.12 (CI, 0.03–0.51) compared with children who were not given supplements—a substantial reduction. This risk reduction was unchanged after adjustment for multiple factors including sex, birth weight, growth rate, gestational age, and maternal reproductive and socioeconomic characteristics. Among infants who were given supplements regularly, those given exactly 50 $\mu\text{g}/\text{day}$ had a relative risk of 0.22 (CI, 0.05–0.89) compared with those given <50 $\mu\text{g}/\text{day}$, and those given >50 $\mu\text{g}/\text{day}$ had a relative risk of 0.14 (CI, 0.02–1.01) compared with those given <50 $\mu\text{g}/\text{day}$. Thus this large, well-designed prospective study provides compelling evidence that vitamin D supplementation of 50 $\mu\text{g}/\text{day}$ or more during infancy may reduce the risk for type 1 diabetes, at least in parts of the world located far north. The potential effectiveness of smaller vitamin D doses cannot be determined from this study.

The findings of these studies are dramatic, and it is clear that the association of infant vitamin D supplementation with diabetes risk should be explored further. However, the applicability of these findings to other settings is uncertain for a number of reasons. First, none of the studies included blood measurements of 25-hydroxyvitamin D (25OHD). The sum of vitamin D obtained from sun exposure and from diet is best characterized by measurements of 25OHD, a liver metabolite of vitamin D and the best indicator of vitamin D stores. Ideally, any study that shows an association of higher compared with lower vitamin D intake would report the 25OHD concentrations of the groups being compared to allow comparisons with populations at different latitudes. One can hypothesize an absolute 25OHD concentration above which the autoimmune response does not occur, whereas identifying a corresponding vitamin D supplement dose would be geographically and demographically dependent. The Hyppönen study, and perhaps also the Stene study, suggests that a rather high vitamin D dose may be necessary to reduce diabetes risk, but none of the studies provides estimates of the effects of vitamin D supplementation below 50 $\mu\text{g}/\text{day}$.

After the time supplementation was given to infants in the Hyppönen study (1966–1967), the recommended vitamin D intake for infants in Finland was reduced from 50 $\mu\text{g}/\text{day}$ to 10 $\mu\text{g}/\text{day}$. This is much closer to the U.S. recommended dietary intake of 5 $\mu\text{g}/\text{day}$ for infants up to one year,¹⁸ and an amount that is consumed by many formula-fed infants. The tolerable upper intake level for infants in the United States has been set at 25 $\mu\text{g}/\text{day}$.¹⁸

Thus, neither U.S. public policy nor current Finnish public policy support supplementation in the only dose ranges shown to be associated with reduced diabetes risk.

What research remains to be done and how should these findings be acted upon in the meantime? The most definitive answer to the vitamin D and type 1 diabetes question would be obtained from a randomized trial that relates several vitamin D supplement doses to diabetes incidence in populations across multiple latitudes, but such a study will probably never be feasible. It may be that further observational studies, conducted in diverse locations, particularly if they include measurements of 25OHD, will adequately define the role of vitamin D in diabetes prevention.

In the meantime, at least in the United States and other areas with comparable sunlight exposure, it would seem prudent to ensure that all infants under age one receive at least the recommended dietary intake of vitamin D, 5 $\mu\text{g}/\text{day}$, especially in winter. Because breast milk provides little vitamin D, infants who are exclusively breastfed require vitamin D supplements to reach this amount. When there is a special concern about diabetes risk, intakes between 5 $\mu\text{g}/\text{day}$ and the 25- $\mu\text{g}/\text{day}$ tolerable upper intake level may be desirable.

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Cellular Transporters for Zinc

Nutritionally essential metals such as zinc are moved into and out of cells by a series of transport proteins or transporters. Their tri-fold purpose is to procure zinc from the environment, to protect cells against zinc toxicity, and maintain ample supplies of zinc for metabolic purposes. Two families of zinc transporters are known: the ZIP family that imports zinc and the ZnT family that functions in releasing zinc or sequestering zinc internally.

Key Words: essential metals, zinc, transport proteins, ZnT, ZIP

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Zinc homeostasis in higher animals and humans is a process that requires cells to move a vanishingly small amount of zinc ions through membranes and into sites for storage or catalysis. A counter measure is to release zinc from absorptive cells as part of a two-step absorption process or as a protective measure against zinc toxicity. Understanding the mechanism of these events at a molecular level has proven a hard task. Early studies generally focused on transport proteins in the blood that literally brought zinc to the transport site in the membrane. Transport models began with zinc already inside the cell. Translocation across the 120-Å membrane was assumed to “just happen,” and once inside, little thought

was given to egress. Now we know that not one, but two families of zinc transporters operate in human cells, a clear indication of a far more complex transport network than initially realized. These specialized proteins import, export, and sequester zinc into vesicles. Although their functions may overlap, their locations, tissue specificities, and responses to dietary zinc are different.

One family of mammalian transporters designated ZnT are comprised of four integral membrane proteins (proteins that penetrate the entire bilayer) with specific groups for attaching and moving zinc (Figure 1). Each

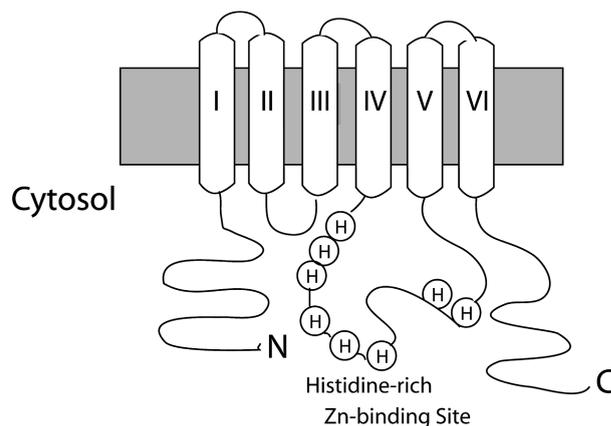


Figure 1. Basic structure of a ZnT zinc transporter. Shown are transmembrane domains (1-VI) through the bilayer that anchor the protein to the membrane and form pores to pass the zinc ions. A histidine-rich loop extends down into the cytosol. The histidine residues are believed to bind the zinc prior to its transport. The protein is positioned to assure unidirectional movement out of the cytosol.

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