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Title: The big Vitamin D mistake

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Abstract

Since 2006, T1D in Finland has been decreasing after an initial plateau preceded by an increase in serum-25OHD after the authorities’ decision for fortification of dietary milk products with cholecalciferol. The role of Vitamin-D in innate and adaptive immunity is critical. A statistical error in the estimation of the Recommended Dietary Allowance (RDA) for Vitamin-D was recently discovered, indicating that 8895 IU/day are needed for 97.5% of individuals to achieve values ≥ 50 nmol/l, analyzing correctly the same data used by the Institute of Medicine. These results were confirmed, showing that 6201 IU/day are needed to achieve 75 nmol/l and 9122 IU/day are needed to reach 100 nmol/l. The largest meta-analysis ever conducted on published studies between January 1966 and January 2013, showed that 25(OH)D < 75 nmol/l may be too low for safety, associated with higher all-cause mortality, demolishing the previously presumed U-shape. Since all-disease mortality is reduced to 1.0 with serum Vitamin-D ≥ 100 nmol/l, we call public health authorities to consider designating, as the RDA, at least 3/4 of the upper tolerable dose proposed by the Endocrine Society Expert Committee as safe upper tolerable daily intake doses: 2000 < 1yr, 4000 1-18yrs and 10,000 IU > 18yrs. This could translate as i.e.1000 IU for children < 1yr on enriched formula and 1500 IU on breast-feeding older than 6 months; 3000 IU for children > 1yr and around 8000 IU for young adults and thereafter. Actions are urgently needed to safely protect global health from Vitamin-D deficiency.
Type 1 Diabetes epidemiology and Vitamin D

Type 1 Diabetes (T1D) incidence has been doubling every 20yrs. In Finland, the recommendation for daily Vitamin-D supplementation was gradually reduced from 4000-5000 IU in 1964 to 400 IU in 1992. Concomitantly, T1D increased 350% in ages 1-4, 100% in 5-9 and 50% in 10-14yrs [1]. But since 2006, T1D has been decreasing after an initial plateau preceded by an increase in serum 25OHD after the authorities’ decision for fortification of all dietary milk products with cholecalciferol [2]. Finally, the worldwide association between UV-B and Vitamin-D status with T1D as well as multiple sclerosis is now more than evident.

Vitamin D and immunomodulation

The role of Vitamin-D in innate and adaptive immunity is critical. It has been shown that redirection of human autoreactive T-cells upon interaction with dendritic cells can be modulated by an analog of 1,25-dihydroxyvitamin D3 [3]. In a most recent plenary session entitled “Cell therapy in Type 1 Diabetes” that closed the European Society for Paediatric Endocrinology 2016 meeting in Paris, Bart O. Roep announced the initiation of phase 1 clinical trials in humans within 2016: dendritic cells will be isolated from the patient’s peripheral blood, will be cultured with calcitriol and then re-injected to an abdominal intradermal position to “teach” the rest of the immune cells not to attack the β-cell anymore. In a large birth cohort study, T1D incidence was reduced by 78% with 2000 IU of cholecalciferol/day [4]. Moreover, T1D autoantibodies can be “negativated” with oral calcitriol [5]. Vitamin-D > 100 nmol/L (40 ng/ml – conversion factor x 2.5) improves insulin secretion [6] and prevents β-cell destruction by suppressing macrophage adhesion-migration through downregulation of the endoplasmic reticulum stress and scavenger receptor-A1 [7].
The statistical error in the estimation of the Recommended Dietary Allowance (RDA) for Vitamin-D

Veugelers PJ and Ekwaru JP analyzing correctly the same data used by the Institute of Medicine (IOM) proved that 8895 IU/day are needed for 97.5% of individuals to achieve values ≥ 50 nmol/l [8]. Then Heaney R et al. confirmed these results [9]: 6201 IU/day are needed to achieve the Endocrine Society’s recommendation of 75 nmol/l and 9122 IU/day to reach 100 nmol/l.

But what are the serum Vitamin-D levels we should be aiming at?

Garland et al. published the largest meta-analysis ever conducted of all published studies between January 1, 1966 and January 15, 2013 referring to all-cause mortality related to serum-25OHD [10], showing that 25(OH)D < 75 nmol/l may be too low for safety, associated with higher all-cause mortality, demolishing the presumed until then U-shape.

Call to public health authorities

Since all-disease (autoimmune diseases, metabolic syndrome, Type 2 Diabetes, cancer) mortality risk is reduced to 1.0 with serum Vitamin-D ≥ 100 nmol/l [10], we call all responsible public health authorities to consider designating, as the RDA (i.e. the average daily level of intake sufficient to meet the nutrient requirements of nearly all healthy people, presuming minimal sun exposure), the proposed by the Endocrine Society Expert Committee (http://dx.doi.org/10.1210/jc.2011-0385) as safe upper tolerable daily intake doses for patients at risk for Vitamin-D deficiency (< 50 nmol/l): 2000 < 1yr, 4000 1-18yrs and 10,000 IU > 18yrs.

Since 9200 IU/day are needed to achieve 100 nmol/l [9], and except Vitamin-D hypersensitivity, and since there is no evidence of adverse effects with serum
25(OH)D < 140 nmol/l, leaving a considerable margin of safety for efforts to raise the population concentration around 100 nmol/l, the doses we propose could be used to reach the level of 75 and preferably that of 100 nmol/l. Of course, the recommended doses can be individualized, considering the self-dietary and sun exposure habits, the latitude of the country, and they can be adjusted to BMI, age and skin color; obese, elderly and dark skinned people needing higher doses.

Explanation of the pandemic of vitamin D deficiency

Only 20% of our vitamin-D reserve is meant to come from the diet. The rest 80% is expected to be produced in our skin from the UV-B of the sun. Compared to the 1960’s recommendations of 4000-5000 IU/day fearing rickets, our diet today is poor in wild fish (x10 richer in Vitamin-D), “wild” eggs and “fresh” milk. Children are playing and people are working all day long indoors and powerful sun-protective cosmetics are used fearing melanoma. Even sunny countries as Greece present high incidence of Vitamin-D deficiency, as the angle the sun rays fall from autumn to spring do not result to sufficient Vitamin-D production with the usual sun exposure.

Optimal Vitamin-D supplementation

With the target for Vitamin-D set at 100 nmol/l, dose, frequency and duration of supplementation will be important factors to healthy subjects committed to optimizing their nutritional status. Since in the case of Vitamin-D, serum levels depend on dietary intake (20%) and sun exposure (80%), a practical approach would be to recommend at least the 3/4 of the upper tolerable dose proposed by the Endocrine Society, to be taken as a supplement all year long except i.e. sunbath vacations. This could translate as i.e.1000 IU for children < 1yr on enriched formula and 1500 IU on breast-feeding older than 6 months; 3000 IU for children > 1yr of age and practically up to 8000 IU
for young adults and thereafter, the latter doses adopted to BMI as proposed by Veugelers et al. with the target being set to 100 instead of 50 nmol/l. More importantly, according to the Endocrine Society’s clinical practice guideline, doses up to 1000 IU/d for infants up to 6 months, 1500 IU/d for infants from 6 months to 1yr, 2500 IU/d for children aged 1–3yr, 3000 IU/d for children aged 4–8yr, and 4000 IU/d for everyone over 8yr can be given safely even without medical supervision just to prevent Vitamin-D deficiency, while higher doses may be needed to correct hypovitaminosis D.

Importance of Vitamin-D supplementation

The importance of such a strategy relies on the adequate supplementation of pregnant and lactating women, and for timely supplementation of every newborn before seroconversion towards autoimmune targets occurs. The benefits on the general health status, apart from the obvious gain on skeletal health, cannot be fully foreseen, but may very well be surprisingly higher than expected given the impact of Vitamin-D deficiency on the metabolic syndrome itself: improvement of the vitamin D status may help reduce the public health burden of metabolic syndrome, and potential subsequent health conditions including type 2 diabetes and cardiovascular disease.

Conclusion

Unfortunately medicine itself took very long to realize that Vitamin-D is not a vitamin that simply prevents rickets. For that purpose, yes, 400-600 IU/day may be enough. But we know today that Vitamin-D is a powerful nuclear-receptor activating hormone of critical importance, especially to the immune system. With the available data mentioned before, the proposed doses would probably suffice to bring and keep Vitamin-D levels around or over 75-100 nmol/l, with practically zero risk for toxicity.
Undeniably, further studies are needed to clarify on the optimal supplementation of Vitamin-D, although it is uncertain whether a universal RDA is feasible. Meanwhile, actions are urgently needed to safely protect global health from Vitamin-D deficiency.

References


