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Vitamin D: Evidence and Controversies: Comment on the Article by Gilaberte et al.

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Abstract Vitamin D deficiency is associated with increased risk of approximately 100 conditions and diseases. Ecological, observational, and cross-sectional studies as well as randomized controlled trials support these associations. Observational studies, with support from the other types, provide the data needed to determine how serum 25-hydroxyvitamin D [25(OH)D] concentration affects disease incidence and mortality rates. The findings for breast and colorectal cancer, respiratory infections, and all-cause mortality rates indicate that benefits increase as serum 25(OH)D concentrations increase to between 75 and 100 nmol/L. Reaching those levels takes up to 5000 IU of vitamin D per day, with considerable individual variation. The main sources of vitamin D that can help people reach those levels are UV-B irradiance and vitamin D_3 supplements. The skin characteristics—both in terms of pigmentation and ability to tan—of most inhabitants of Spain are ideally suited for regular moderate solar UV irradiance. In general, melanoma risk is low in southern Europe. Risk of nonmelanoma skin cancer is higher, but such cancers are seldom fatal, and a study in Denmark found a 9% reduction in 10-year all-cause mortality rate for patients diagnosed with basal cell carcinoma.

PALABRAS CLAVE
Vitamina D;
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Vitamina D: Evidencia y Controversias: comentarios sobre el artículo de Gilaberte et al.

Resumen La deficiencia de Vitamina D se asocia con un riesgo aumentado de unas 100 condiciones y enfermedades. Estudios ecológicos, observacionales y trasversales así como ensayos controlados y randomizados apoyan estas asociaciones. Estudios observacionales, con el apoyo de otros tipos, proporcionan los datos necesarios para determinar como la concentración en suero de 25-hidroxivitamina D (25[OH]D) afecta la incidencia de enfermedad y las tasas de mortalidad. Los datos sobre carcinoma colorrectal y mama así como la tasa de mortalidad por todas las causas indican que los beneficios aumentan con niveles de 25(OH)D entre 75 y 100 nmol/L.

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Para alcanzar estos niveles, hacen falta unas 5.000 UI de vitamina D por día, con bastante variación individual. Las fuentes principales de la vitamina D que puede ayudar a las personas a alcanzar estos niveles son la radiación UV-B y los suplementos de vitamina D_3. Las características de la piel- tanto en términos de pigmentación como de capacidad para broncearse - de la mayoría de los habitantes de España son muy adecuadas para una moderada exposición al sol. En general, el riesgo de melanoma es bajo en el sur de Europa. El riesgo de cáncer de piel no melanoma es más alto, aunque tales cánceres no suelen conllevar mortalidad. Un estudio de Dinamarca encontró una reducción del 9% en la tasa de mortalidad por todas las causas en 10 años para pacientes diagnosticados de carcinoma basocelular.

Introduction

The recent review in this journal serves as a good introduction to the controversies surrounding scientific findings and policy recommendations regarding vitamin D, its health benefits, requirements for optimal health, and how to obtain adequate vitamin D[1]. The literature is full of contradictory findings, opinions, and recommendations, so unless one has studied it carefully for an extended period making sense of it at face value is difficult. The crux of the problem is that, because of inherent or practical limitations, different types of studies can arrive at different conclusions. This commentary on the work of Gilaberte and colleagues offers more insight into how to assess and interpret the literature on vitamin D and UV irradiance.

Studies of vitamin D deficiency and disease outcomes

There are several ways of determining the role of vitamin D deficiency in the risk of disease. Ecological studies—which investigate the relationship between geographical variation in disease outcomes and the risk-modifying factors for each geographical unit of population or seasonal variation—can be useful in identifying and quantifying relationships between solar UV-B doses and disease outcome. The ecological approach has linked low solar UV-B doses to about 20 types of cancer.[2] The time-varying ecological study approach has linked solar UV-B to reduced risk of influenza.[3]

Observational studies can be either case–control studies, which measure serum 25-hydroxyvitamin D [25(OH)D] concentrations at time of diagnosis, or nested case–control studies derived from cohort studies. Cohort studies compare patients who have the disease with similar healthy controls, grouping the disease by quantiles of 25(OH)D concentration. Case–control studies find stronger inverse correlations between 25(OH)D concentration and disease incidence because nested case–control studies measure vitamin D status with a single serum 25(OH)D concentration at time of enrollment; over time, this sole measure becomes less reliable.[4]

Cross-sectional studies are snapshots of health conditions and biometric values made by random sampling of the population.

In randomized controlled trials (RCTs), some participants receive the agent and others a placebo. Participants are followed up for weeks to years, and health outcomes, both positive and negative, are noted. Using RCTs to study the effects of vitamin D on disease outcome poses many problems: the dose is often inadequate, compliance may be poor, other sources of vitamin D exist, and serum 25(OH)D response to oral vitamin D intake varies considerably from person to person.[5]

Vitamin D requirements

With this background, we can now address how vitamin D requirements can and should be determined. Relationships between serum 25(OH)D concentration and disease outcome are essential. Ecological studies provide indirect information because they use indices of solar UV-B dose. RCTs generally use a single dose and so have difficulty representing the entire relationship unless several such studies are included in a meta-analysis or in a pooled analysis. That leaves observational studies, which use serum 25(OH)D concentrations and generally provide 4–5 values for serum 25(OH)D concentration to use in determining relative risk (RR), hazard ratio or odds ratio (OR). Because single observational studies have large uncertainties, several observational studies should be combined in either a pooled analysis or a meta-analysis.

In an earlier work, I recently combined observational studies of breast and colorectal cancer incidence with respect to serum 25(OH)D concentration in meta-analyses.[6] Values from various studies were combined by overlaying the values such that the center of the regression fit to each study overlapped. Then the values were combined into a single data set and fit with a power law function. For breast cancer, the OR decreased from unity at 22 nmol/L to about 0.43 near 100 nmol/L, with little apparent change at higher values. For colorectal cancer, the OR dropped from unity near 12 nmol/L to 0.32 at 100 nmol/L. In both cases, the OR decreased rapidly at first and then more slowly at higher 25(OH)D concentrations.

I previously reported a similar analysis for cardiovascular disease. The third-order fit to the data found the hazard ratio decreasing from unity near 18 nmol/L to 0.51 at 100 nmol/L, with little change at higher values.[7]

In an observational study, those with serum 25(OH)D concentrations below 95 nmol/L had an increased risk of acute respiratory infections, whereas those with higher levels did not.[8]

More recently, a rigorous meta-analysis examined all-cause mortality rate as a function of serum 25(OH)D concentration at time of enrollment in 11 studies.[9] The second-order fit to the RR decreased from unity at an assu-

med value of 27.5 nmol/L to 0.68 at 80 nmol/L and then started to increase. However, the 95% confidence interval at 80 nmol/L extended from 0.60 to 0.78 and increased in deviation from the RR at values up to 115 nmol/L, so it is not clear whether the upturn is real.

Thus, from the observational and cross-sectional studies, the optimal serum 25(OH)D concentration—defined as the point at which the data currently available no longer show improved health outcome—is between 75 nmol/L and 100 nmol/L. This is the same as the range determined by vitamin D experts at a meeting in Paris in September 2009.[10]

Recommendations

Ideally, vitamin D recommendations would be made based on the best scientific evidence available, with review by vitamin D experts and subject to peer review. The Intergovernmental Panel on Climate Change used that approach to assess the evidence regarding climate change. At least 1000 climate change researchers prepared the *IPCC Fourth Assessment Report: Climate Change 2007*[11] and another thousand reviewed it. Unfortunately, the Institute of Medicine's Committee to Review Dietary Reference Intakes for Vitamin D and Calcium was composed of 14 scientists with expertise in nutrition, but varied expertise regarding vitamin D. The committee prepared a report,[12] limiting its review to selected RCTs, and solicited—but ignored and refused to make public—peer reviews of the final document. Thus, this document lacks the kind of scientific authority that would be expected for such an important topic.

After the Institute of Medicine released this report, the US Endocrine Society recommended a vitamin D level of at least 75 nmol/L.[13]

Vitamin D confers important benefits during pregnancy. Serum 25(OH)D concentrations above 75–100 nmol/L greatly reduce the risk of bacterial vaginosis, preeclampsia, primary Cesarean delivery, premature birth, low birth weight, birth defects, and rickets.[14] A recent RCT involving pregnant and nursing women in South Carolina found that 4000 IU of vitamin D_3 per day was generally required to reach optimal serum 25(OH)D and 1,25-dihydroxyvitamin D concentrations and have enough unconverted vitamin D_3 available in breast milk for the infant.[15] No adverse effects, such as changes in serum or urine calcium concentrations, occurred.

Benefits of optimal 25(OH)D concentrations

The health benefits of vitamin D extend from better pregnancy and birth outcomes[14] to reduced risk of many types of cancer,[2] cardiovascular disease,[7,16,17] diabetes,[16] respiratory infections,[3,8] and many other conditions and diseases (for more information see http://www.vitamindcouncil.org/health-conditions/).

The 25(OH)D concentration–disease outcome relations have been used to estimate how raising population mean serum 25(OH)D concentrations from 50–55 nmol/L to 100–110 nmol/L would reduce mortality rates for countries and continents. The study for the United States found that doing so could avoid approximately 400 000 premature deaths per year,[18] representing 17% of all deaths. A worldwide study found mortality rate reductions of 8%–17%, increasing worldwide life expectancy by 2 years.[7]

UV irradiance

Solar UV-B irradiance is the primary source of vitamin D for most people on Earth. Skin pigmentation has adapted to the prevailing solar UV doses in places where humans have lived for thousands of years. As descendants of a long line of Spaniards, modern Spaniards' skin is well adapted to solar radiation in Spain: dark enough to protect against the adverse effects without sunscreen yet light enough to permit adequate production of vitamin D.[19] One adaptation to life in mid-latitudes is the ability to tan, which increases protection against UV irradiance by a factor of 2–4.[19]

Several studies offer evidence that Spaniards can and should experience solar UV-B with strong benefits and limited risks. In an ecological study of cancer mortality rates in Spain during 1978–1992, nonmelanoma skin cancer mortality rates were inversely correlated with 15 types of cancer, including melanoma for females.[20] Mortality rates for nonmelanoma skin cancer were much lower than the all-cancer mortality rate.

Many people are concerned about the risk of melanoma from solar UV irradiance. However, those exposed to the sun occupationally have no greater risk of developing melanoma than those who are not so exposed.[21] Risk of melanoma is associated with intermittent UV irradiance[21] and sunburn.

Another risk factor associated with solar UV irradiance is development of basal cell carcinoma or squamous cell carcinoma. A study in Denmark found that those who developed basal cell carcinoma had a lower mortality rate than those who did not (10-year RR = 0.91 [95% confidence interval, 0.89–0.92]).[22]

Producing vitamin D from solar U-VB irradiance in the summer is easy. The important considerations are solar zenith angle (for optimal production, the sun should be within 45 degrees of being overhead), the amount of surface area exposed, time in the sun, and age. With whole-body exposure, one can make at least 10,000 IU of vitamin D_3 in less time than it would take to develop erythema (redness).

Conclusions

This review offers considerable evidence that higher serum 25(OH)D concentrations would greatly reduce the risk of disease and increase life expectancy in Spain. It would be worthwhile for health policy makers in Spain to review the evidence, with input from UV irradiance and vitamin D researchers in Spain and elsewhere, and then make recommendations for public policy.

Conflicts of interest

Dr. William Grant has received funding from the UV Foundation (McLean, VA), Bio-Tech Pharmacal (Fayetteville, AR), the Vitamin D Council (San Luis Obispo, CA), and the Vitamin D Society (Canada).

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