Journal of Steroid Biochemistry & Molecular Biology 121 (2010) 456–458

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry and Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Health benefits of higher serum 25-hydroxyvitamin D levels in The Netherlands☆

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ARTICLE INFO

Article history:
Received 29 October 2009
Received in revised form 29 March 2010
Accepted 30 March 2010

Keywords:
Cancer
Cardiovascular disease
Cathelicidin
Infectious diseases
Ultraviolet-B
Vitamin D

ABSTRACT

A large and rapidly expanding body of scientific literature exists on the roles of vitamin D in maintaining optimal health and reducing the risk of chronic and infectious diseases. Serum 25-hydroxyvitamin D [25(OH)D] levels for optimal health are in the range of 100–150 nmol/L; mean population values in The Netherlands are around 50–63 nmol/L. Health problems for which there exists good observational evidence and some randomized controlled trial evidence that vitamin D reduces risk include many types of cancer, cardiovascular disease, diabetes mellitus, bacterial and viral infections, autoimmune diseases, osteoporosis, falls and fractures, dementia, congestive heart failure, and adverse pregnancy outcomes. Reductions in incidence and mortality rates for various diseases and all-cause mortality rates can be determined from ecological, observational and cross-sectional studies and randomized controlled trials. For The Netherlands, raising mean serum 25(OH)D levels to 105 nmol/L is estimated to reduce specific disease rates by 10–50% and all-cause mortality rates by 18%. To raise serum 25(OH)D levels by this amount, inhabitants in The Netherlands would have to increase vitamin D production or oral intake by 2500–4000 IU/day. Doing so would pose only minimal increased risks of melanoma or skin cancer or hypercalcemia.

1. Introduction

A large and rapidly expanding body of scientific literature exists on the roles of vitamin D in maintaining optimal health and reducing the risk of chronic and infectious diseases [1,2]. Historically, vitamin D was obtained primarily by the action of solar ultraviolet-B (UVB) radiation hitting 7-dehydrocholesterol in the lower epidermis, followed by a thermal process. After the initial production, vitamin D is transported to the liver, where it receives a hydroxyl group and becomes 25-hydroxyvitamin D [25(OH)D], the primary circulating vitamin D metabolite. Then the kidneys and many other organs convert 25(OH)D to 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the hormonal version that can activate vitamin D receptors and thereby gene expression, and induce production of human cathelicidin, LL-37, which has important antimicrobial and antiendotoxin properties [3]. The importance of vitamin D is underscored by the fact that skin pigmentation of indigenous peoples varies according to ambient solar UV doses [4].

The optimal serum 25(OH)D level appears to be in the range of 100–150 nmol/L on the basis of meta-analyses of observational studies [5,6], randomized controlled trials (RCTs) [8], and cross-sectional studies [8,9]. In The Netherlands, the population mean serum 25(OH)D level for free living elderly living in Amsterdam in 1995–1996 was 50–55 nmol/L (20–22 ng/mL) [10]. For each 1000 IU/day of vitamin D, serum 25(OH)D levels rise by 15–25 nmol/L [7,11]. Thus, the daily vitamin D production or oral intake required to increase the mean serum 25(OH)D level in The Netherlands from 50 to 105 nmol/L is 2500–4000 IU/day.

Because the population mean serum 25(OH)D level in The Netherlands is far below that for optimal health, significant reductions in incidence and mortality rates for many types of disease would probably occur if the mean serum level was raised as indicated. Indeed, similar studies for Western Europe [12] and Canada [6] indicate that mortality rates can be reduced by 10–20% and the economic burden of disease reduced by about 10%. The aim of this report is to estimate the reduction in disease-specific and all-cause mortality rates in The Netherlands by the indicated increase in serum 25(OH)D levels.

The estimates of reductions in mortality rates in this study are based on findings reported in observational and cross-sectional studies and RCTs, with limited reference to ecological studies and hypothesis papers. Although RCTs would be the preferred type of study to use, there have been few well-conducted RCTs that used a sufficient dose of vitamin D to obtain significant reductions in disease risk, with 400 IU/day standard until recently [13]. Also, RCTs

☆ Special issue selected article from the 14th Vitamin D Workshop held at Brugge, Belgium on October 4–8, 2009.

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doi:10.1016/j.jsbmb.2010.03.089

Table 1
Estimated reduction in mortality rates for vitamin D-sensitive diseases in the Netherlands if mean population serum 25(OH)D levels were raised to 42 ng/mL (105 nmol/L) based on 2002 mortality rates [44].

Disease	Mortality rate (deaths/100,000/year) [44]	Vitamin D reduction (%)	Reference	Avoided mortality rate, expected, minimum, maximum (deaths/100,000/year)
Cancers	248	25 (15–35)	[5–7]	62 (37–87)
Cardiovascular disease	313	25 (15–35)	[8,14–17]	78 (47–110)
Diabetes	22	15 (10–20)	[8,18–20]	3 (2–5)
Multiple sclerosis	1.3	50 (40–60)	[21]	0.7 (0.5–0.8)
Lower airway	50	30 (20–40)	[22,23]	15 (10–20)
Falls and fractures	4.6	20 (10–30)	[24]	0.9 (0.5–1.4)
Other causes	228			
All causes	868	18 (11–25)		160 (97–223)

do not generally use death as the disease endpoint but, rather, incidence. Vitamin D most probably has different effects on incidence and death rates.

2. Results

The diseases that this study considers include cancers, cardiovascular disease, diabetes, multiple sclerosis, lower airway respiratory diseases, and falls and fractures. Together, these diseases have high mortality rates in The Netherlands. More information on all these conditions—including the results of more studies as well as the mechanisms whereby vitamin D reduces the risk of each disease—is given in Grant [12] and Grant et al. [6].

Table 1 gives the estimated reductions in mortality rates. The estimates range from 10% for dementia (not mentioned in Table 1), from a hypothesis paper [25], to 50% for multiple sclerosis, from the fact that Epstein–Barr virus infection seems to be the most important risk factor and that vitamin D greatly reduces the risk of Epstein–Barr virus infection's progressing to multiple sclerosis [21]. Use of vitamin D could avoid an estimated premature mortality rate of 117 deaths/100,000/year, representing 23% of the all-cause mortality rate, with an estimated uncertainty ranging from 80 to 153 deaths/100,000/year.

3. Discussion

The estimate of 18% reduction in all-cause mortality rate is similar to that reported in a cross-sectional study in the United States. In that study of 3408 persons older than 65 years at time of enrollment and followed up for a median of 7.3 years, the modeled hazard ratio for 10–20 ng/mL compared with more than 100 nmol/L was 1.47 (95% confidence interval, 1.09–1.97), whereas that for 50–75 nmol/L compared with more than 100 nmol/L was 1.21 (95% confidence interval, 0.92–1.59) [9]. Thus, the estimates given in Table 1 have a reasonable confidence level. Health problems for which no estimates were given but that are also linked to low serum 25(OH)D levels include congestive heart failure [26], septicemia [27], and dementia [25].

If the results are valid, what would we recommend to the health and medical authorities of The Netherlands? The first step might be to use this and related studies and redo on the short term the recent publication by the Health Council of The Netherlands, *Towards an Adequate Intake of Vitamin D* [28]. It is puzzling why European countries, including The Netherlands, do not recognize observational studies as part of body of evidence and are so reluctant to embrace the mounting evidence of the substantial benefits of vitamin D for health promotion. Although a working group of the International Agency for Research on Cancer (IARC) dismissed evidence of a beneficial role of vitamin D for all cancers other than colon cancer [29], the working group consisted largely of those concerned about protecting people from melanoma and nonmelanoma skin cancer, so they were biased against studies reporting a beneficial role of either UVB or vitamin D [30]. There is also a reluctance to change paradigms in general, and vitamin D in particular [31].

The next step might be to work with other countries within the European Community to adopt guidelines for the higher fortification of food and permit an increase of the vitamin D content in dietary supplements on basis of a proper risk benefit analysis. Because many people in Europe are either lactose intolerant, especially in southern countries, or gluten intolerant, especially in northern countries, both dairy and grain products could be fortified with vitamin D. For a discussion of food fortification, see [32,33]. Oral intake levels of 1000–4000 IU/day are beneficial for 99% of the population [34], with primarily those having granulomatous diseases or hematopoietic cancers at risk of developing hypercalcemia at lower doses [35].

Solar and artificial UVB should also be considered good sources of vitamin D. A recent analysis calculated that if inhabitants of the United States relied upon solar UVB to increase serum 25(OH)D levels from 63 to 105 nmol/L, the health benefits would greatly exceed the increased risk of melanoma and nonmelanoma skin cancer [36]. Sunbeds are also a good source of vitamin D, as shown by a study in Norway [37]. Those used in Europe have influences similar to midday summer solar UV in the Mediterranean area, and can generate 10,000 IU of vitamin D in about 20 min for a young person with Fitzpatrick skin type 2. Those who have occupational or chronic ultraviolet irradiance do not have an increased risk of melanoma, whereas those who undergo recreational irradiance do [38]. Consistent use of solar or artificial UVB sources for vitamin D production should not, therefore, increase the risk of melanoma, although those with type 1 Fitzpatrick skin should limit UV irradiance. The meta-analysis of melanoma risk associated with ever use of sunbeds reported by the IARC, odds ratio = 1.15 (95% CI, 1.00–1.30) [39], was flawed in that several studies from the UK were included for which no adjustment was made for skin type. Many residents in the UK have the allele of the melanocortin receptor 1 (MC1R) gene [40] that is an important risk factor for melanoma [41]. When the five UK studies are removed, the odds ratio falls by 0.10 and is no longer statistically significant [42]. However, a recent prospective study of melanoma with respect to sunbed use in Sweden found approximately 50% increased risk of melanoma for more than 2–3 sunbed uses per week for those aged 20–39 years [43], the health benefits of solar UVB irradiance greatly outweigh this risk [36]. Sunbed use in Sweden was found inversely correlated with endometrial cancer and thrombotic events [42].

Acknowledgments

This report was funded by a grant to SUNARC by the Sunlight Research Forum (Veldhoven). SUNARC also receives funding from the UV Foundation (McLean, VA), the Vitamin D Society (Canada), and Bio-Tech Pharmacal (Fayetteville, AR).

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