Estimation of the Benefits of Raising Mean Serum 25-Hydroxyvitamin D Levels to 100-115 nmol/L World Wide

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Abstract. The understanding of the health benefits of solar ultraviolet B (UVB) irradiance and vitamin D is expanding rapidly based on a combination of ecological, observational, cross-sectional, laboratory, and clinical studies and randomized controlled trials (RCTs). The strongest evidence for non-calcemic effects is for many types of cancer and several types of infectious and autoimmune diseases. Encouraging and generally consistent findings have been reported for cardiovascular, metabolic, and neurological diseases and congestive heart failure. The serum level for optimal health has been reported to be 100-150 nmol/L (40-60 ng/mL) in observational studies, meta-analyses of such studies, and RCTs. The benefits of raising mean population serum 25-hydroxyvitamin D [25(OH)D] levels from 40-63 nmol/L to 100-113 nmol/L can be estimated based on estimated dose-response relations for various diseases and incidence or mortality rates for these diseases. This abstract presents an overview of the approach and representative findings for several countries.

Basis for 100-113 nmol/L

Various ecological and observational studies and randomized controlled trials provide evidence for using 100-113 nmol/L as the target level for benefits. One reason is that the mean serum 25(OH)D level of the highest quantile in observational studies is near there. Some examples:

Meta-analyses of cardiovascular disease and diabetes incidence [Parker, 2010].

Randomized controlled trial of vitamin D supplementation and type A influenza incidence [Urashima et al., 2010].

Seventeen vitamin D-sensitive cancers with strong support**,** primarily from ecological studies, with some observational studies, for incidence and/or mortality:

Blood: Hodgkin's and non-Hodgkin's lymphoma;
Female: breast, endometrial, ovarian, vulvar;
Gastrointestinal: colon, esophageal, gallbladder, gastric, pancreatic, rectal;
Male: prostate;
Urinary: bladder, renal;
Miscellaneous: lung, melanoma.

Evidence for cancer

The evidence for a beneficial role of UVB and vitamin D in reducing the risk of cancer and the dose-response relation is based on numerous studies, with ecological and observational studies covering many types of cancer [Giovannucci et al., 2006; Grant and Garland, 2006; Grant, 2007].

The serum 25(OH)D level-cancer incidence relation has been developed for breast cancer using five prospective studies referenced to prediagnostic serum 25(OH)D levels [Abbas et al., 2008, 2009; Bertone-Johnson et al., 2005; Crew et al., 2009; Freedman et al., 2008; Lowe et al., 2005]. The data for mean serum 25(OH)D levels for the quantiles in the study from 22 to 153 nmol/L were fit to a power law with the equation odds ratio (OR) = $7.41x[25(OH)D]^{-0.603}$ (p=0.91) [Grant, submitted]. A similar relation was found for colorectal cancer: OR = $3.95x[25(OH)D]^{-0.541}$ (p=0.77) [Grant, submitted].

Evidence for cardiovascular disease

The evidence of a beneficial effect of vitamin D in reducing the risk of cardiovascular disease is primarily from prospective observational studies. Using data from six recent studies [Dobnig, 2008; Ginde, 2009; Giovannucci, 2008; Kilkkinen, 2009; Melamed, 2008; Semba, 2009]. A power law fit to the data yields the finding hazard ratio = $5.22x[25(OH)D]^{-0.425}$ (p=0.87) [Grant, unpublished].

Evidence for all-cause mortality rate

The evidence of a beneficial effect of vitamin D in reducing the risk of cardiovascular disease is primarily from prospective observational studies. Using data from four recent studies [Dobnig, 2008; Melamed, 2008; Ginde, 2009; Semba, 2009]. A power law fit to the data yields the finding hazard ratio = $4.46x[25(OH)D]^{-0.396}$ (p=0.95) [Grant, unpublished].

Estimate for a benefit of increasing serum 25(OH)D levels for Western Europe

Such serum 25(OH)D level-disease outcome relations can be used to estimate the reductions in mortality rates and economic burden of disease for countries or regions. The approach taken is to first determine the mean serum 25(OH)D level for the population, then use the level-outcome relations to estimate the reductions in disease outcome for the change in serum 25(OH)D level. While the percentage effect on mortality rate and economic burden from an increase in serum 25(OH)D level may not be the same as for incidence, this approach is a good starting point.

The estimate for the avoided premature death rate for Western Europe for increasing serum 25(OH)D levels from 50-63 nmol/L to 100 nmol/L is presented in Table 1.

Similar analyses have also been performed for other countries. A summary of such findings is given in Table 2.

Table 1. Estimate of avoided death rates for Western Europe for 2002 from increasing mean serum 25(OH)D levels from 50-63 nmol/L to 100 nmol/L (Grant et al., 2009).

Disease	Mortality rate*	Reduction **(%)	Avoided mortality rate*
Cancers	39.8	25	10.0 (6.0-14.0)
CVD	171.2	15	25.7 (8.6-42.8)
Dementia	17.0	10	1.7 (0.0-3.4)
Diabetes	12.4	15	1.9 (0.6-3.1)
MS	1.0	50	0.5 (0.4-0.6)
Lower airway infection	24.8	20	5.0 (2.5-7.4)
COPD, asthma	24.3	10	2.4 (0.0-4.9)
Other	97.7	0?	0?
Totals	388.2	12 (5-20)	47.2 (18.1-76.2)

* deaths/100,000/year;
** uncertainty estimated at ±10 from given value; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; MS, multiple sclerosis

Table 2. Estimates of reduction in mortality rates from increasing serum 25(OH)D levels to 100 nmol/L for several countries.

Country	Rate	Avoided rate	Avoid (%)	Reference
Australia	417	61 (29-91)	15 (9-22)	
Canada	446	61 (30-93)	14 (7-21)	Grant et al. 2010
Netherlands	504	92 (55-128)	18 (11-25)	Grant, Schuite-maker, in press
USA	544	63 (34-113)	13 (6-21)	Grant, 2009

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