ANTICANCER RESEARCH *36*: 1379-1388 (2016)

Review

Vitamin D and Mortality

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Abstract. *In this narrative review, we aim to summarize and discuss the current evidence linking vitamin D and mortality. Low 25-hydroxyvitamin D [25(OH)D] concentrations are associated with an increased risk of mortality. This has been shown in different cohort studies including general populations, as well as various patient cohorts. Some single-study results and meta-analyses indicate that the shape of the relationship between 25(OH)D and mortality follows a U- or a reverse J-shaped curve. Interassay and laboratory differences are, however, a limitation of most previous surveys, and standardization of 25(OH)D measurements is needed for future investigations. Apart from observational data, it has been documented in meta-analyses of randomized controlled trials that vitamin D3 supplementation is associated with a moderate, yet statistically significant, reduction in mortality. This latter finding must be interpreted in light of some limitations such as incomplete follow-up data, but such a reduction of mortality with vitamin D_3 supplementation as the finding of meta-analyses of randomized controlled trials strongly argues for the benefits and, importantly, also the safety of vitamin D.*

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Key Words: Vitamin D, mortality, RCT, epidemiology, 25(OH)D, review.

Vitamin D deficiency is recognized as a public health problem because low vitamin D levels are common, and may contribute to various adverse health outcomes (1-4). Beneficial effects of vitamin D for skeletal health, *i.e.* prevention and treatment of rickets and osteomalacia, as well as anti-fracture effects, were considered to be a sufficient basis for guidelines on Dietary Reference Intakes (DRI) and Dietary Reference Values (DRV) for vitamin D in Europe and North America (5-9). Vitamin D deficiency has also been associated with several extraskeletal diseases such as cancer, infections, and cardiovascular, autoimmune and neuropsychiatric diseases (1-5). Importantly, accumulating evidence suggests that vitamin D deficiency might contribute to premature death.

In this narrative review, we aim to summarize and discuss current evidence linking vitamin D and mortality. We start with a brief introduction on vitamin D metabolism, classic vitamin D effects, and current approaches for laboratory measurements and treatment of vitamin D deficiency. Then we present data on the association between serum 25-hydroxyvitamin D [25(OH)D] and mortality, and will also cover genetic data, *i.e.* Mendelian randomization studies, on this topic. We summarize and discuss current evidence from randomized controlled trials (RCTs) on the effects of vitamin D supplementation on mortality. We also briefly outline data on vitamin D and cause-specific death. Finally, we provide

an outlook on ongoing research with regard to overall health implications of vitamin D deficiency and the potential approaches on how to deal with this issue from a public health perspective.

Vitamin D Metabolism and Classic Effects of Vitamin D

The major source for vitamin D is ultraviolet-B (sunlight)-induced vitamin D synthesis in the skin. In detail, the liver-derived precursor of vitamin D, 7-dehydrocholesterol, is converted to vitamin D in the epidermis under the influence of ultraviolet-B radiation. Nutrition usually contains only minor amounts of vitamin D. Transport of vitamin D metabolites in the circulation is mainly performed by its binding to the vitamin D-binding protein (DBP). In the liver, vitamin D is hydroxylated to 25(OH)D, the major circulating vitamin D metabolite that is used to classify vitamin D status. Further 1α-hydroxylation of 25(OH)D results in the formation of 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], the so-called active vitamin D hormone or calcitriol. The kidneys are the major site for 1,25$(OH)_2$D formation but 1α-hydroxylase expression has also been detected in several types of extrarenal cells and organs, suggesting a local tissue production of 1,25$(OH)_2$D that seems to be mainly dependent on substrate availability of circulating 25(OH)D (10). Effects of 1,25(OH)2D are mediated via binding to the vitamin D receptor (VDR) that is expressed in almost all human cells and regulates approximately 3% of the human genome (11).

Assessment of vitamin D status is carried out by measuring serum levels of 25(OH)D. It has, however, been increasingly recognized that significant assay and laboratory differences exist with regard to the measurement of 25(OH)D (12, 13). Therefore, there is an urgent need for further standardization of laboratory methods with initiatives such as the Vitamin D Standardization Program (12, 13). Caution is, however, warranted when comparing 25(OH)D values derived from different laboratories or assays.

Vitamin D effects are required for physiological bone and mineral metabolism, and one of the major effects of vitamin D, also from an evolutionary perspective, is to ensure adequate calcium supply for bone mineralization thereby preventing rickets and osteomalacia (14-16). In meta-analyses of RCTs it has been documented that vitamin D supplementation can significantly reduce fractures (17, 18). Bischoff-Ferrari *et al*. showed that a daily vitamin D dose of approximately 800 to 2,000 International Units (IU) (20 to 50 μg) per day is required to achieve this anti-fracture effect (17). Vitamin D supplementation is thus a standard treatment for patients suffering from osteoporosis (19). It is still not entirely clear by through pathways vitamin D reduces fractures, but accumulating evidence suggests that fall prevention by vitamin D may, at least partially, be responsible for the anti-fracture effect (19-22).

With regard to guidelines and recommendations for vitamin D intakes and supplementation, there exists controversy in the literature concerning vitamin D doses and target levels for 25(OH)D (6-9, 23-27). 25(OH)D concentrations of 50 nmol/l (divide by 2.496 to convert nmol/l to ng/ml) are, however, widely considered as sufficient, and can be achieved in almost all individuals of the general population, even in absence of sunlight exposure, when supplementing 800 IU (20 μg) vitamin D per day (8, 9). Therefore, when endogenous vitamin D synthesis is absent, *e.g*. during winter in Germany, vitamin D intake of 800 IU (20 μg) is recommended for the general population (8). Actual vitamin D intake by nutrition and supplements is, however, usually below 200 IU (5 μg) per day in the vast majority of the general population (28-30). Consequently, significant parts of the general population have serum 25(OH)D concentrations below 50 nmol/l (31, 32). When considering the potential public health consequences of vitamin D deficiency, it is of great concern that there is a huge gap between official dietary recommendations and actual intakes of vitamin D. It is, thus, of public health interest to further evaluate whether the proposed involvement of vitamin D in several diseases contributes to premature mortality in vitamin D-deficient individuals.

Vitamin D Status and Mortality

The vast majority of prospective observational studies showed that individuals at the lower end of the 25(OH)D distribution are at significantly increased risk of mortality (33-53). These data have been derived from investigations in the general populations, as well as in various different patient cohorts (33-46). In meta-analyses, the effect estimates for the increase in mortality in individuals with vitamin D deficiency ranged from approximately 40 to 90% when comparing groups with the lowest *versus* the highest (reference) 25(OH)D levels (34, 41, 43, 44, 47). The largest meta-analysis including 849,412 study participants from 73 cohort studies with 66,511 mortality events was conducted by Chowdhury *et al*. (44). In that study, the relative risk (RR) [with 95% confidence interval (CI)] for mortality, adjusted for potential risk factors, in the bottom *versus* the top third of baseline 25(OH)D levels was 1.35 (1.22 to 1.49). Comparing participants with 25(OH)D <25 nmol/l *versus* those with ≥75 nmol/l, the RR (95% CI) was 1.50 (1.21 to 1.87). Assuming a linear relationship between vitamin D status and mortality, each decrease in 25(OH)D of 25 nmol/l was associated with a 16% (95% CI=8-23%) increase in all-cause mortality. Importantly, the association between 25(OH)D and mortality was similar across various subgroups analyses. The

second largest meta-analysis was performed by Garland *et al*. and included over 500,000 study individuals (47, 53). In that work, the hazard ratio (95% CI) for mortality in participants with 25(OH)D levels ≤22.5 nmol/l compared to those with >75 nmol/l was 1.9 (1.6 to 2.2).

While meta-analyses of epidemiological studies have consistently confirmed that individuals with low 25(OH)D concentrations are at increased risk of mortality, the precise shape of the 25(OH)D–mortality curve is still not entirely clear. Some studies reported on a U- or reverse J- shaped curve for the 25(OH)D and mortality relationship, while others did not (45-53). The reports on U- or reverse J-shaped curves raised the questions of which 25(OH)D levels at the lower (and higher) end are associated with increased mortality, and which levels are optimal. Most observational studies performed their statistical analyses on mortality risk according to a few 25(OH)D groups (*e.g*. quartiles), and were therefore not adequately designed to evaluate the 25(OH)D–mortality curve in detail. To address this issue, Sempos *et al*. analyzed 15-year follow-up data of the Third National Health and Nutrition Examination Survey including 15,099 individuals of whom 3,784 died (52). They observed a reverse J-shaped association between 25(OH)D and mortality with a steep upswing for levels below 40 nmol/l. Compared to the reference group with 25(OH)D levels of 75-99 nmol/l, individuals with 25(OH)D concentrations of 120 nmol/l or more were at higher risk of mortality, but the level of statistical significance was only achieved in some statistical models and disappeared in the fully adjusted analyses. In the same work, the lowest mortality risk was observed at levels of 81 nmol/l. In line with this, the meta-analysis by Zittermann *et al*. in 62,548 individuals of the general population reported the lowest mortality risk for individuals with 25(OH)D serum concentrations ranging from 75-87.5 nmol/l. In that meta-analysis, the 25(OH)D–mortality relationship curve resembled a reverse J-shaped curve (41). There was, however, no statistically significantly increased risk of mortality in individuals with the highest 25(OH)D concentrations, but mortality risk was only estimated up to levels of 112.5 nmol/l (41). While it has been hypothesized that one explanation for the reverse J-shaped curve may be that individuals with high 25(OH)D concentrations started to take vitamin D supplements but were previously vitamin D deficient, it must also be underlined that it is well established that vitamin D can be toxic at very high doses, leading to life-threatening conditions with hypercalcemia and calcification (50, 52-54). Hypercalcemia, as the hallmark of vitamin D intoxication, however, only occurs at 25(OH)D levels above ~375 to 500 nmol/l and thus with extreme overdosing of vitamin D. Considering that 25(OH)D levels up to approximately 125 nmol/l can be considered relatively safe, there is a wide range of 25(OH)D levels, *i.e*. from 125-375 nmol/l, for which there are insufficient data on whether and by which mechanisms these levels could be harmful.

When reviewing and discussing the 25(OH)D–mortality relationship, it must be acknowledged that a major limitation of most observational studies is the lack of standardization of laboratory measurements of 25(OH)D (12). Caution is therefore warranted when interpreting and discussing absolute 25(OH)D values that are derived from different laboratory methods. Moreover, published meta-analyses are, with the exception of the work by Schöttker *et al*., limited by using the conventional meta-analysis approach of analyzing literature-based study results (43, 55). Individual participant data (IPD) meta-analyses are superior compared to these classic literature-based meta-analyses as they aim to harmonize data *e.g*. with regard to grouping, adjustments and statistical approaches of the individual studies (55). Therefore, further IPD meta-analyses on 25(OH)D and mortality are urgently needed that should include studies with standardized 25(OH)D measurements and calculate regression curves for the 25(OH)D–mortality relationship that are not only based on groups (*e.g*. quartiles) but on IPD data of each single individual.

In addition to these findings on 25(OH)D and mortality, it should also be mentioned that in some, albeit not all, studies, low sunlight exposure and low levels of 1,25(OH)2D have been associated with an increased mortality (56-62). These issues, which extend the scope of our work have been well reported elsewhere (56-62).

Vitamin D Genetics and Mortality

Genome-wide association studies have identified genetic loci that are associated with circulating 25(OH)D concentrations (63, 64). These genetic loci encode genes with relevance for vitamin D synthesis, *i.e*. for synthesis of vitamin D precursors [7-dehydrocholesterol reductase (*DHCR7*)] and vitamin D 25-hydroxlyation [cytochrome P450 2R1 (*CYP2R1*)], as well as for vitamin D metabolism, *i.e*. for vitamin D transport by DBP [group-specific component (GC)] and 24-hydroxylation (*CYP24A1*). These genetic variants can be used to conduct Mendelian randomization studies that evaluate whether the genetically determined variation of a risk marker, *e.g*. 25(OH)D, is associated with outcome (*e.g*. mortality) (65). Assuming that the genetic variations for 25(OH)D are not associated with confounding factors, Mendelian randomization studies are useful for evaluating whether an association is causal (66, 67). Moreover, the use of such genetic data has the advantage over RCTs that lifelong exposure is tested, whereas RCTs have a limited intervention time. In this context, Afzal *et al*. performed a Mendelian randomization study to evaluate whether genetically low 25(OH)D levels are associated with increased mortality (68). They included 95,766 White participants of Danish descent

and used genetic variants of *DHCR7* and *CYP2R1* for their study. For plasma 25(OH)D concentrations, each decrease of 20 nmol/l was associated with an adjusted odds ratio for mortality of 1.21 (95% CI=1.11 to 1.31), thus confirming the established association between vitamin D deficiency and increased mortality. Interestingly, for genetically determined 25(OH)D concentrations, each decrease of 20 nmol/l was associated with an odds ratio of 1.30 (95% CI=1.05-1.61). Therefore, there was no significant difference for the association with mortality between the genetically determined and the measured plasma 25(OH)D levels. These findings suggest that the association between low 25(OH)D and mortality may be causal.

Vitamin D Supplementation and Mortality

In addition to the above mentioned observational data, meta-analyses of RCTs have found that vitamin D3 supplementation reduces overall mortality (44, 69-71). In a Cochrane meta-analysis, Bjelakovic *et al*. included 56 trials with 95,286 study participants (69). In detail, they included RCTs comparing any type of vitamin D supplementation (*i.e*. vitamin D3, vitamin D2, and active vitamin D or its analogs) *versus* placebo or no intervention. The study participants of the included trials were, in the majority, older women and the mean treatment duration was 4.4 years. Vitamin D of any type reduced mortality with a risk ratio (95% CI) of 0.97 (0.94 to 0.99), but among the different forms of vitamin D, only vitamin D3 treatment was associated with a significantly reduced mortality and a risk ratio (95% CI) of 0.94 (0.91 to 0.98). Based on this finding, it was further calculated that 150 individuals need to be treated with vitamin D_3 over 5 years to prevent one death. There were no significant differences for the effect of vitamin D_3 on mortality in various sensitivity/sub-group analyses. Rejnmark *et al*. (70) and Bolland *et al*. (71) reported on similar effects of vitamin D on mortality. Chowdury *et al*. restricted their meta-analysis to randomized trials that supplemented natural vitamin D (vitamin D_3 or D_2) alone without any concomitant intervention such as *e.g*. calcium (44). They included 30,716 study participants and found that vitamin D_3, but not vitamin D_2, reduced mortality significantly, with a risk ratio of 0.89 (95% CI=0.80 to 0.99). Although these findings on vitamin D3 and mortality were statistically significant, it must be noted that due to *e.g*. incomplete follow-up data of the analyzed RCTs and some other limitations, it is still not entirely clear whether this reflects a true effect. Nevertheless, a reduction in mortality within a background of vitamin D supplementation according to meta-analyses of RCTs provides a strong rationale in favor of the benefits and safety of vitamin D intake. This notion is underlined by a recent RCT in patients in intensive care units (72). In that RCT, Amrein *et al*. included 492 critically ill patients with 25(OH)D concentrations ≤50 nmol/l who were randomly allocated to vitamin D_3 at a dose of 540,000 IU followed by monthly maintenance doses of 90,000 IU vitamin D_3 for 5 months or placebo. There was no significant effect on mortality and several other outcomes in the whole study population, but in a pre-specified sub-group analysis of patients with 25(OH)D levels ≤30 nmol/l, hospital mortality was significantly reduced in the vitamin D-supplemented group compared to the placebo-treated group, with a hazard ratio (95% CI) of 0.56 (0.35 to 0.90).

Vitamin D and Specific Causes of Death

While we mainly report on vitamin D and all-cause mortality in this review, it is also important to briefly summarize the literature on specific causes of death, in order to gain more knowledge on the potential pathways and mechanisms that may link vitamin D and fatal events.

In observational studies, low 25(OH)D levels have been associated with increased risk of mortality due to cardiovascular diseases, cancer, respiratory disease, and non-vascular, non-cancer causes (33, 35, 36, 43, 44, 49, 73-76).

In the Mendelian randomization study by Afzal *et al*. it was reported that the odds ratio (95% CI) for cardiovascular mortality for each decrease of 20 nmol/l in plasma 25(OH)D was 1.13 (1.03 to 1.24), and the respective odds ratio (95% CI) for the genetically determined 25(OH)D levels was 0.77 (0.55 to 1.08) (68). This may suggest that the association between low 25(OH)D and cardiovascular deaths may not be causal. For cancer mortality, the respective odds ratios (95% CI) for each decrease of 20 nmol/l 25(OH)D was 1.10 (1.02 to 1.19) for plasma 25(OH)D and 1.43 (1.02 to 1.99) for genetically determined 25(OH)D. These data argue for causality with regard to the association of vitamin D deficiency and increased cancer mortality.

Meta-analyses of RCTs further support a causal effect of vitamin D on cancer mortality. In the Cochrane meta-analysis by Bjelakovic *et al*. involving 44,492 study participants from four trials, it was documented that vitamin D_3 supplementation statistically significantly reduced cancer mortality, with a risk ratio of 0.88 (95% CI=0.78-0.98). In line with this, Keum *et al*. also reported in their meta-analysis involving 44,260 participants that the RR for cancer mortality in the vitamin D-treated *versus* the placebo-treated group was 0.88 (95% CI=0.78-0.98) (77). These findings along with various molecular anticancer effects of vitamin D suggest that vitamin D supplementation may be useful for the prevention of cancer deaths. By contrast, there was no effect in meta-analyses on cancer incidence, suggesting that vitamin D might rather be relevant for the progression than for the initiation of cancer (77-79).

With regard to cardiovascular mortality, there was no significant effect of vitamin D as reported by Bjelakovic *et*

al. (69). Although observational studies highlight vitamin D deficiency as a risk factor for cardiovascular events and strokes, most RCTs did not show any effect of vitamin D on these outcomes (69, 71, 80-83). It must, however, be acknowledged that no published RCT on vitamin D has been designed and statistically powered to assess cardiovascular events. Existing knowledge on the potential role of vitamin D for various other health outcomes have been extensively reviewed elsewhere (1-6, 84, 85).

Outlook and Conclusion

Vitamin D deficiency is a risk factor for increased mortality and meta-analyses of randomized trials suggest that vitamin D_3 supplementation may reduce mortality. These data along with the established effects of vitamin D on skeletal health point towards the urgent need to prevent and treat vitamin D deficiency in the general population.

The actual vitamin D intake in the general population is far below the recommended DRI for vitamin D, thus contributing to a relatively high prevalence of vitamin D deficiency. Therefore, there is an urgent need for public health approaches to improve vitamin D status. A 'healthy lifestyle' with outdoor activities involving careful and balanced sunlight exposure along with efforts to combat the global burden of obesity would, without any dietary vitamin D interventions, substantially improve 25(OH)D levels in the general population (9, 87-91). Being aware that changing lifestyle is hard to achieve, it is clear that additional efforts are required to increase oral vitamin D intake by diet and/or supplements. A promising approach is vitamin D food fortification that has already been introduced in countries such as Finland and the US. Work such as the EU project ODIN, Food-based Solutions for Optimal Vitamin D Nutrition and Health Throughout the Life Cycle (http://www.odin-vitd.eu/), is currently in progress to further investigate (and hopefully introduce) vitamin D food fortification in general populations throughout the EU (9, 86). Moreover, some expert groups are also suggesting vitamin D supplement intake for groups at high risk of vitamin D deficiency, and a recent study on cost-effectiveness of vitamin D supplementation calculated that treating the elderly UK population with 800 IU vitamin D_3 per day would translate into substantial cost-savings through fall prevention (26, 87). Elucidating safe and efficient approaches to eradicate vitamin D deficiency is a challenge for public health authorities and should be a goal with a high priority when considering the potential and the risk–benefit ratio of vitamin D supplementation for improvement of public health and health economics.

Regarding vitamin D research, there are some large ongoing RCTs on vitamin D in the general population that will significantly increase our knowledge on whether general vitamin D supplementation in the older population has an effect on clinical endpoints, including mortality (92, 93). It is, however, of concern that all large RCTs on vitamin D recruited participants regardless of their 25(OH)D levels, thereby increasing the probability of missing beneficial effects of vitamin D supplementation in individuals with low 25(OH)D concentrations. Null effects of such RCTs would definitely argue against major effect sizes but definite answers on whether vitamin D supplementation has relevant effects on mortality outcomes and other clinical endpoints should be derived from RCTs in severely vitamin D-deficient individuals, as this is the target population for vitamin D interventions (92-95).

Acknowledgements

Martin Gaksch is supported by the EU project ODIN (FFood-based Solutions for Optimal Vitamin D Nutrition and Health Throughout the Life Cycle; FP7-KBBE-2013-7-single-stage; Grant agreement no: 613977).

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Received November 30, 2015
Revised January 12, 2016
Accepted January 14, 2016