Maturitas xxx (2011) xxx–xxx

Contents lists available at ScienceDirect

Maturitas

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

Vitamin D and aging: Beyond calcium and bone metabolism

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ARTICLE INFO

Article history:
Received 4 February 2011
Accepted 9 February 2011
Available online xxx

Keywords:
Aging
Vitamin D
Mortality
Frailty
Vitamin D polymorphisms
1,25-Dihydroxyvitamin D
25-Hydroxyvitamin D
Vitamin D receptor

ABSTRACT

Background: Low serum 25-hydroxyvitamin D (25[OH]D) levels are common and may be associated with morbidity and mortality (and indeed with frailty more generally). This association is not restricted to the links between vitamin D and calcium and bone metabolism.
Objective: To review the influences of vitamin D on the aging process other than those related to bone and calcium. Its effect on mortality is also assessed.
Methods: The PubMed database was searched for English-language articles relating to vitamin D, using the following MeSH terms: vitamin D, mortality, cardiovascular diseases, and frailty. In addition, searches were carried out with Google.
Results: Although some of the reported results have proved controversial, overall the evidence seems to support an association between low serum 25[OH]D levels and mortality rates (all-cause and cardiovascular). Frailty is a condition frequently associated with low serum 25[OH]D levels.
Conclusion: The aging process and mortality are associated with low vitamin D levels. Prospective controlled trials are warranted to determine whether vitamin D supplements can increase longevity and reduce the incidence of certain conditions.

Contents

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doi:10.1016/j.maturitas.2011.02.014

1. Introduction

Some 750 million years ago marine plankton steroid molecules were first broken down by sunlight, and vitamin D-related secosteroid compounds have been incorporated into the alimentary chain of complex marine ecosystems ever since. When terrestrial life emerged some 250 million years ago, the development of a rigid skeletal structure despite the scarcity of environmental calcium became a major evolutionary challenge. Under this scenario, the development of the vitamin D system became a pivotal adaptive mechanism.

During the first half of the 20th century, more than 80% of children in industrialized Western countries had rickets [1,2]. Its prevalence significantly decreased when it became evident that exposure to ultraviolet (UV) light was a major source of vitamin D and food and supplements were fortified with vitamin D. Nevertheless, modern lifestyles and diets and the use of sunscreens have led to a recurrence of a high prevalence of low vitamin D status [3]. A low vitamin D status may be present for many years, starting from intrauterine life and continuing into childhood, adult life, maturity and older age [3–9].

Vitamin D deficiency may cause secondary hyperparathyroidism and increase bone resorption [10,11]. Raised serum levels of parathyroid hormone (PTH) produce phosphaturia and hypophosphatemia, which induce defective osteoid mineralization (osteomalacia). Low serum vitamin D levels are also associated with osteoporosis and fracture risk [7,12]. Low vitamin D levels may also be involved in other age-related diseases, including infections, cancer and cardiovascular, autoimmune and neurodegenerative diseases. Morbid conditions related to low vitamin D levels are likely to be mediated by genomic and epigenetic mechanisms other than the conventional calcium–bone axis and PTH-related homeostasis. Using new DNA sequencing technology, Ramagopalan et al. [13] created a map of vitamin D receptors (VDRs) along the genome, and found 2776 sites that specifically bind vitamin D and exert protein expression. Many of these sites are located near genes linked to autoimmune diseases, cancers and other conditions.

Such findings emphasize the importance of adequate vitamin D levels to human health. In view of vitamin D's possible involvement in many age-related health conditions, the role of 1,25-dihydroxyvitamin D (1,25-dihydroxy-cholecalciferol, $1,25[OH]_2D$) or calcitriol in humans is of growing interest. The present paper reviews some of the influences of vitamin D in the aging process other than those related to bone and calcium.

2. The vitamin D endocrine system

Human vitamin D_3 (cholecalciferol) is synthesized from cholesterol by the action of UVB (290–315 nm) sunlight on the skin. This accounts for 90% of the body's vitamin D supply. Cholecalciferol and ergocalciferol (vitamin D_2) may also be acquired from the diet. Vitamin D is then transformed by the liver into 25-hydroxyvitamin D (25-hydroxycholecalciferol, 25[OH]D) or calcidiol. Serum 25[OH]D concentration is the best indicator of vitamin D status (deficiency or sufficiency). The half-life of 25[OH]D in plasma is approximately 2–3 weeks. Renal and extra-renal 1-α-hydroxylase activity transforms 25[OH]D into the biologically active form, $1,25[OH]_2D$ (Fig. 1). There is no risk of endogenous $1,25[OH]_2D$ overstimulation due to the biological protection produced by a 24-hydroxylation system that inactivates both 25[OH]D and $1,25[OH]_2D$. The latter (the active form of the vitamin) acts mainly on the duodenum, increasing calcium absorption. It also acts on bone cells (osteoblasts and osteoclasts) to mobilize calcium.

Free $1,25[OH]_2D$ enters cells mostly by diffusion and binding to complex VDRs, which are widely distributed in almost all cell types [3,4]. A liganded VDR undergoes conformational change and forms a heterodimer with a second protein, the retinoid X receptor. This, in turn, binds to DNA response elements in the promoter regions of target genes. The biological effects of $1,25[OH]_2D$ are primarily mediated through interaction with VDRs (Fig. 1). However, there are also non-genomic effects, which are more rapid; these include kinase and phosphatase activation and phosphoinositide metabolism, as well as an influence on cytosolic calcium levels and other biochemical pathways [14].

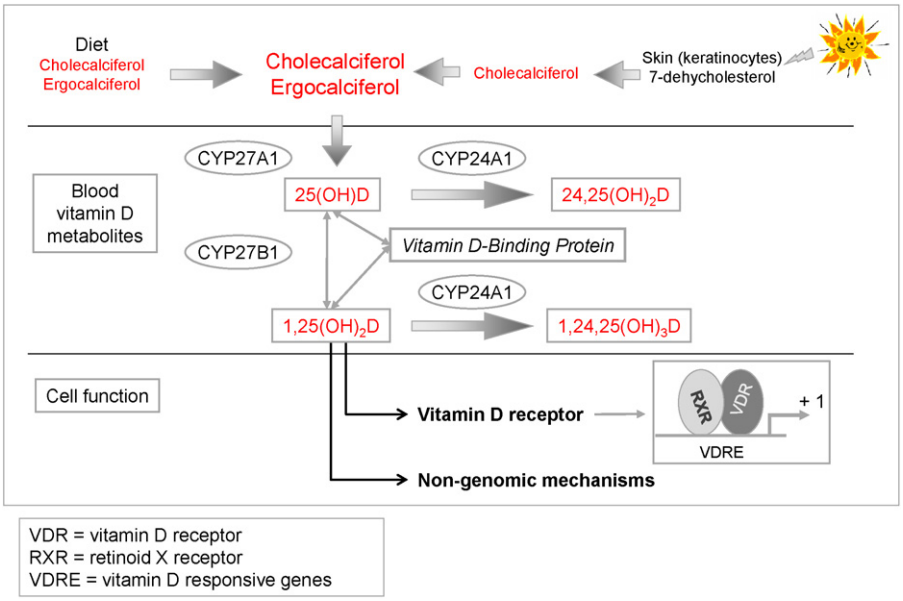

Fig. 1. Vitamin D acquisition by skin photosynthesis and digestive absorption. Blood metabolites include 25[OH]D produced by the liver, which is bound to the vitamin D-binding protein. Renal and extra-renal tissue 1alpha-hydroxylation produces the bioactive compound $1,25[OH]_2D$. The excess of 25[OH]D and $1,25[OH]_2D$ is inactivated by a 24-hydroxilation enzymatic system. $1,25[OH]_2D$ enters most cell types binding to its VDR, forming a heterodimer with the retinoid X receptor. This complex binds to DNA response elements within target genes. $1,25[OH]_2D$ also has non-genomic actions.

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Serum 25[OH]D levels above 30 ng/mL (75 nmol/L) have been suggested as desirable. Levels below this cut-off point have been associated with alterations in bone mineral metabolism, fractures, falls, cancer, cardiovascular disease (CVD), hypertension, metabolic syndrome, infections and immune dysfunction.

3. Vitamin D intake and mortality

Studies have reported in recent years that vitamin D deficiencies may be associated with a higher risk of death due to CVD, cancer or other chronic diseases (in total, these conditions account for 60–70% of deaths in high-income countries). It has been hypothesized, although not yet proven, that high endogenous vitamin D levels can increase life expectancy. Autier and Gandini [15] reported a meta-analysis of 18 studies. Individuals who took vitamin D at daily doses ranging from 300 to 2000 IU (average dose 528 IU) for an average of 5.7 years had a 7% lower risk of death (from all causes) than those who did not. The editorial that accompanied the report of the meta-analysis suggested that the relatively low dose of vitamin D and the short treatment period may have led to an underestimation of its effect on the clinical evolution of chronic conditions such as CVD and cancer, as well as of the overall improvement in the immune system and of the vascular protection afforded [16].

A systematic review of 17 prospective studies and randomized trials examining supplementation with vitamin D, calcium, or both and subsequent cardiovascular events concluded that vitamin D supplementation may reduce the risk of CVD. Calcium supplementation seems to have minimal cardiovascular effects, and indeed four prospective studies that included initially healthy subjects reported no differences in the incidence of CVD between calcium supplement recipients and non-recipients. Separate analysis of the 8 randomized trials found a non-significant reduction in CVD risk with vitamin D supplementation, whereas no effect was found with calcium or the combined (vitamin D and calcium) supplementation [17].

4. Serum vitamin D levels and mortality

4.1. All-cause and cardiovascular mortality

The importance of vitamin D metabolism for the cardiovascular system and mortality risk has been reviewed in recent years [9,18–21]. Many studies have produced evidence of an association between low serum 25[OH]D levels and all-cause and CVD-related mortality rates (Table 1). Most studies have compared quartiles – or other fractions – and baseline or follow-up vitamin D status.

The Third National Health and Nutrition Examination Survey (NHANES III) reported that low serum 25[OH]D levels in adults (aged 20 years or more) were associated with mortality [19]. Multivariate analysis found that low serum vitamin D levels (lowest quartile) were independently associated with aging, female gender, non-white ethnicity, diabetes, current smoking, and higher body mass index. After 8.7 years of follow-up (median), individuals with serum 25[OH]D levels in the lowest quartile had a 26% increased rate of all-cause mortality and a population attributable risk of 3.1%. Although not reaching statistical significance, in this analysis the adjusted models for CVD and cancer-related mortality risks were higher in the quintile with the lowest serum 25[OH]D levels.

The association of serum 25[OH]D levels with cardiovascular mortality and its contribution to elevated risk among black individuals were assessed in a posterior, retrospective and more detailed re-analysis of the NHANES III cohort [22]. Individuals were surveyed between 1988 and 1994 and cause-specific mortality was determined through to 2001 using the National Death Index. Risk of cardiovascular death was analyzed using regression models assessing 25[OH]D quartiles, adjusting for cardiovascular risk factors, and these models were compared in terms of the adjusted race-related cardiovascular mortality with and without further adjustment for 25[OH]D levels. Individuals with 25[OH]D levels in the lowest quartile (mean 13.9 ng/mL) had a higher adjusted risk of cardiovascular death than those in the other three quartiles. In addition, the higher mortality observed among blacks than whites was attenuated by 25[OH]D adjustment, and fully eliminated when income adjustment was included.

A subsequent NHANES III publication that included only individuals aged 65 years or more ($n = 3408$) found independent inverse associations between serum 25[OH]D levels and CVD and all-cause mortality after 7.3 years (median) of follow-up [23]. Compared with individuals with serum 25[OH]D levels 100 nmol/L or higher, adjusted hazard ratios (HRs) for all-cause mortality were 1.83 and 1.47 for those with levels <25 nmol/L and 25.0–49.9 nmol/L, respectively; this association was stronger for CVD mortality (adjusted HR = 2.36) than for non-CVD mortality (adjusted HR = 1.42) in those with lower vitamin D levels. A more recent analysis of the NHANES III cohort [24], reporting follow-up of 14 years and dividing individuals according to skin characteristics, found that baseline serum 25[OH]D levels were linked to fatal stroke. Serum 25[OH]D levels below 15 ng/mL were observed in 6.6% of whites, compared with 32.3% of blacks. Individuals deficient in vitamin D had a twofold increased risk of fatal stroke. This association was not observed among blacks. The study was based on a single vitamin D measurement (and so was not necessarily representative of lifetime vitamin D values) and non-fatal strokes or other ischemic possibilities were not assessed. These may been seen as limitations of the study. The unexpected results concerning black individuals were interpreted as some unknown resistance or adaptation mechanism.

The relationship between 25[OH]D and all-cause mortality was reported in the Société de Secours Minière de Bourgogne, Montceau les Mines, France (MINOS) study, a cohort of men aged 50 years or more followed up for 10 years [25]. Non-survivors were older, and had more co-morbidities and lower physical performance. Mortality within the initial 3 years was predicted among subjects in the lowest quartile of serum 25[OH]D levels; no relationship was found between mortality and age, body mass index, smoking, physical activity, vitamin D supplementation or health status. Neither did testosterone or PTH levels predict mortality.

Results from a prospective Austrian cohort of 3258 patients followed up for 7.7 years (median) and referred for coronary angiography were reported by Dobnig et al. [26]. Patients underwent detailed baseline examinations, including serum 25[OH]D measurements. Individuals with baseline 25[OH]D levels in the lower two quartiles (median 7.6 and 13.3 ng/mL) and those in the lowest $1,25[OH]_2D$ quartile displayed a significantly higher risk of all-cause mortality. Low 25[OH]D levels correlated with markers of inflammation (C-reactive protein and interleukin 6), oxidative burden (serum phospholipid and glutathione), and cell adhesion (vascular cell adhesion molecule-1 and intercellular adhesion molecule-1). This biochemical information suggests that vitamin D exerts an anti-inflammatory and anti-oxidative effect on the vascular adhesion system.

The relationship between 25[OH]D and all-cause and cardiovascular mortality in older women and men after 6.2 years (mean) of follow-up has also been analyzed in a prospective population study [27]. Individuals in the lowest 25[OH]D quartile had higher rates of all-cause and CVD mortality than did those in the other three 25[OH]D quartiles, in both unadjusted and adjusted analyses.

The Italian prospective InCHIANTI (*Invecchiare in Chianti, Aging in the Chianti Area*) cohort study reported a link between low serum 25[OH]D levels and all-cause and CVD mortality. That study fol-

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Table 1
Serum vitamin D levels and mortality (all-cause, CVD and other chronic conditions) according to country and studied population.

Authors	Country	Population	Comments
Melamed et al. [19]	USA	NHANES III: 13,331 adults, 20 years and older, and 8.7 years (median) follow-up	The lowest quartile of serum 25(OH)D levels was associated with all-cause mortality
Ginde et al. [23]	USA	NHANES III: 3408 non-institutionalized individuals, 65 years and older and 7.3 years (median) follow-up	Serum 25(OH)D levels are inversely associated with CVD and all-cause mortality
Fiscella and Franks [22]	USA	NHANES III:15,363 individuals aged 18 years and older	Subjects with serum 25(OH)D levels in the lowest quartile had higher risk of cardiovascular death. The higher age- and sex-adjusted cardiovascular mortality observed in blacks vs. whites was attenuated by adjustment for 25(OH)D levels and fully eliminated with further adjustment for income
Michos [24]	USA	NHANES III: 7981 white and black adults with no history of CVD and stroke and 14 years (mean) follow-up	Serum 25(OH)D deficient individuals had a twofold increased risk of fatal stroke mortality as compared to those with optimal levels, whereas there was no association between 25(OH)D levels and fatal stroke among blacks
Szulc et al. [25]	France	MINOS study: 782 men 50 years and older, followed-up 10 years	Increased estradiol levels predicted mortality whereas low 25(OH)D levels weakly predicted all-cause mortality
Dobnig et al. [26]	Austria	3258 individuals 62 ± 10 years scheduled for coronary angiography at a single tertiary center followed-up 7.7 years (median)	Subjects with serum 25(OH) D levels in the lower two quartiles were at higher risk for all-cause and CVD mortality
Pilz et al. [27]	Austria	614 individuals from the population-based Hoorn Study: mean follow up 6.2 years	Individuals with serum 25(OH)D levels in the low quartile was associated with all-cause mortality and even more with cardiovascular mortality
Semba et al. [28]	Italy	1006 individuals aged 65 years or more from the InCHIANTI study and 6.5 years follow up	Subjects with serum 25(OH)D levels in the lowest quartile had increased risk of all-cause and CVD mortality
Hutchinson et al. [29]	Norway	7161 participants of the Tromsø Study and a mean 11.7 year follow-up	There was a significant increased risk of all-cause mortality among non-smokers with serum 25(OH)D levels in the lowest quartile. There were no differences in mortality for smokers
Kikkinen et al. [30]	Finland	6219 individuals 30 years and older from the Mini-Finland Health Survey and 25 years follow-up	CVD mortality was significantly higher in subjects with serum 25(OH)D levels in the lowest quintile as compared to the highest quintile; the association was significant for cerebrovascular death but not for coronary death
Virtanen et al. [31]	Finland	1136 individuals 53–73 years free of CVD and cancer at baseline from the Kuopio Ischaemic Heart Disease Risk Factor Study and a mean 9.1 year follow-up	All-cause mortality was higher for those with serum 25(OH)D levels in the low tertile
Michaëlsson et al. [32]	Sweden	1194 elderly men, 71 years (mean) at baseline from the Uppsala Longitudinal Study of Adult Men and followed-up 12.7 years (median)	Serum 25(OH)D levels and total mortality displayed a U-shape association, with an approximately 50% higher mortality rate among men in the lowest 10% (<46 nmol/L) and the highest 5% (>98 nmol/L) of plasma 25(OH)D levels compared with intermediate concentrations. Cancer mortality also displayed a U-shaped association with 25(OH)D levels
Liu et al. [33]	Netherlands	548 patients with heart failure, 71 years (mean) and a 33% mean left ventricular ejection fraction	Lower serum 25(OH)D levels were associated with an increased risk for all-cause mortality and combined endpoint mortality/heart failure re-hospitalization
Cawthon et al. [34]	USA	1490 community-dwelling men at least 65 years of age and 7.3 years of follow-up	There was no association between serum 25(OH)D levels and all-cause and cardiovascular mortality; unexpectedly lower 25(OH)D levels were slightly associated with a decreased cancer mortality risk
Joergensen et al. [35]	Denmark	289 type 2 diabetic patients with different degrees of albuminuria, followed-up for 15 years	All-cause and cardiovascular mortality were increased in diabetics with serum 25(OH)D levels in the lower 10th percentile, independent of urinary albumin excretion rate
Eaton [37]	USA	2429 postmenopausal women included in the Women's Health Initiative	All-cause and cardiovascular mortality were increased in the lowest serum 25(OH)D, although this did not reach significance
Jassal et al. [38]	USA	1073 community-dwelling older adults from the Rancho Bernardo Study, followed up for 10.4 years (mean 6.4)	No significant associations were found between 25(OH)D, $1,25(OH)_2D$, or intact PTH levels and cardiovascular mortality
Freedman et al. [40]	USA	16,818 individuals in the NHANES III 17 years or older, followed up for more than 16 years	Cancer mortality was unrelated to baseline 25(OH)D levels. Nevertheless colorectal cancer mortality displayed an inverse relation with serum 25(OH)D levels
Freedman et al. [42]	USA	16,819 individuals of the NHANES III	Overall cancer mortality risks were unrelated to baseline 25(OH)D status, although cancer mortality in females was inversely associated with 25(OH)D in the summer/higher latitude group
Drechsler et al. [44]	Germany	1108 hemodialysis diabetics, 66 years (mean), from the German Diabetes and Dialysis Study, followed up for a median of 4 years	Diabetics with 25(OH)D levels ≤25 nmol/L had a 3-fold higher risk of sudden cardiac death as compared to those with levels >75 nmol/L; cardiovascular events and all-cause mortality were strongly increased in subjects with the lower values

NHANES III, Third National Health and Nutrition Examination Survey; MINOS, Société de Secours Minière de Bourgogne, Montceau les Mines, France; InCHIANTI, Invecchiare in Chianti, Aging in the Chianti Area.

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lowed 1006 adults aged 65 years or more for a median 6.5 years [28]. After adjusting for age, sex, education, season, physical activity and other confounders, individuals with 25[OH]D levels in the lowest quartile (<10.5 ng/mL) displayed a significantly higher risk of all-cause (HR = 2.11) and CVD (HR = 2.64) mortality.

After following up 7161 individuals for 11.7 years, the Tromsø study reported a significant increase in all-cause mortality risk (HR = 1.32) among non-smokers in the quartile with the lowest serum 25[OH]D levels compared with the quartile with the highest levels, but no differences observed for smokers [29].

The Mini-Finland Health Survey evaluated the value of 25[OH]D serum determination in predicting CVD mortality. The study included 6219 men and women aged 30 or more and free from CVD at baseline [30]. The HRs for total CVD-related death (0.76) and cerebrovascular-related death (0.48) were significantly lower for individuals with 25[OH]D levels in the highest quintile in comparison with the lowest one. However, no differences were observed for coronary-related death. More recently, a population-based Finnish cohort reported that serum 25[OH]D concentrations were associated with all-cause and cardiovascular mortality. The cohort included individuals free of CVD and cancer at baseline. After a mean 9.1-year follow-up and adjustments, the HR for death (of any cause) was greater in the tertile with lowest 25[OH]D levels [31].

The association between 25[OH]D levels and total mortality was reported in an Uppsala community-based cohort of elderly men (mean age 71 years at baseline) followed up for 12.7 years. Mortality rates were increased among individuals with the lowest and highest 25[OH]D levels (that is, the mortality–vitamin D curve had a U shape) [32]. In another report, the cancer mortality rate was also high at both higher and lower 25[OH]D levels. Cardiovascular-related death was, though, associated only with low vitamin D levels.

Serum 25[OH]D levels have been used to predict survival among heart failure patients [33]. The authors studied renin activity and 25[OH]D and cytokine levels in 548 cases. Patients with lower vitamin D concentrations presented higher risk rates of death or re-hospitalization. In addition, significant correlations were found between levels of 25[OH]D, renin activity and C-reactive protein, which supports an association between low vitamin D levels and activation of the renin–angiotensin system and altered cytokine levels.

Cawthon et al. [34] reported that low 25[OH]D and high PTH levels may increase the mortality risk in men aged at least 65 years, after 7.3 years of follow-up. The authors found no association between 25[OH]D levels and cardiovascular or other-cause mortality. Contrary to this, high PTH levels were associated with increased all-cause mortality.

Severe 25[OH]D deficiency predicted all-cause and cardiovascular mortality among type 2 diabetic patients, regardless of urinary albumin excretion rate [35]. A small group of these diabetic patients were followed up for 15 years (median) and those with 25[OH]D serum levels below 13.9 nmol/L (the lowest 10th percentile) had a twofold increased risk for all-cause and cardiovascular mortality even after adjusting for diabetes duration, glycated hemoglobin status, kidney function and cardiovascular risk factors. The authors postulated that vitamin D may suppress the renin–angiotensin–aldosterone system, cardiac hypertrophy and vascular calcification, decreasing the risk of certain cancers as well. These results, though, express association, and do not have etiological implications.

Counter to all the aforementioned studies, others have failed to find an association between vitamin D levels and mortality. For example, the Women's Health Initiative (WHI) trial found no benefit in vitamin D supplementation [36], although methodological limitations to this study have been noted [7]. Investigators from the WHI analyzed data from 2429 postmenopausal women who had undergone cardiovascular monitoring for more than 10 years. It was reported that individuals in the quartile with the lowest 25[OH]D levels, as compared with the highest, did display an increased risk for all-cause and cardiovascular mortality (62%, HR = 1.62; and 92%, HR = 1.92, respectively), but this the relationship did not attain statistical significance after adjusting for confounding variables such as age, ethnicity, hypertension, smoking, CVD, diabetes and others (adjusted HR = 1.27 [all cause] and HR = 1.30 [cardiovascular mortality]). Researchers recognized misclassifications, non-random sampling and non-measurement of confounding factors [37], potential limitations previously discussed in relation to other topics [7].

The Rancho Bernardo prospective cohort reported no relationship between 25[OH]D (mean 42 ng/mL), $1,25[OH]_2D$ and PTH levels and cardiovascular mortality [38]. Central obesity (waist circumference) was a possible confounding factor. The results highlight the fact that future studies should include body measurements to determine the causative role of vitamin D in morbid conditions and mortality.

4.2. Chronic disease-related mortality

A meta-analysis of 63 observational studies addressed the relationship between vitamin D levels and cancer incidence and mortality [39]. Twenty of 30 studies assessing vitamin D and colon cancer found that individuals with higher vitamin D levels had either a lower incidence of colon cancer or decreased mortality. Similarly, 9 of 13 studies examining breast cancer and 13 of 26 examining prostate cancer provided evidence of a beneficial effect of vitamin D levels on incidence or mortality (some of the studies included more than one type of cancer).

Serum 25[OH]D levels in relation to cancer incidence, survival and mortality have been studied in the NHANES III cohort [40]. While total cancer mortality was unrelated to baseline 25[OH]D levels in the study population, colorectal cancer mortality was related to serum 25[OH]D levels: individuals with 25[OH]D levels of 80 nmol/L or more had lower colorectal cancer mortality rates than those with levels below 50 nmol/L. The NHANES III study has been criticized, though, and one reanalysis found a significantly lower breast cancer mortality rate among women with 25[OH]D serum levels above the median (62.5 nmol/L) [41]. Serum 25[OH]D levels in relation to total cancer mortality risk were also analyzed in a further NHANES III study, in both sexes, by ethnicity and site-specific cancer [42]. In this large series, cancer mortality risks were again unrelated to basal 25[OH]D levels. Nonetheless, the risk was significantly decreased among women in the summer/higher latitude group presenting with 25[OH]D levels >37.5 nmol/L, compared with women with lower levels. Contrary to this, mortality related to certain cancers was higher in men with higher 25[OH]D levels.

Dose–response effects on colorectal, breast and prostate cancer have been reviewed in a recent meta-regression analysis of observational studies that included 25[OH]D measurements [43]. A total of 35 independent studies were identified. The summary relative risk for a 10 ng/mL increase in serum 25[OH]D was 0.85 for colorectal cancer, 0.89 for breast cancer, and 0.99 for prostate cancer. Hence, it seems that 25[OH]D levels display a consistent inverse relationship with colorectal cancer.

The impact of serum 25[OH]D levels on cardiovascular outcomes was studied in diabetic hemodialysis patients included in the German Diabetes and Dialysis Study [44]. In this population, individuals with 25[OH]D levels $\leq$25 nmol/L had a 3-fold higher risk of sudden cardiac death compared with those with levels 75 nmol/L or higher (HR = 2.99). Cardiovascular events and all-cause mortality were also increased (HR = 1.78 and 1.74, respectively). In addition,

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there were borderline non-significant associations with stroke and fatal infections.

Overall, it seems there is evidence of a positive effect of higher serum vitamin D levels on longevity. However, randomized prospective studies analyzing vitamin D supplementation are still lacking. Trials under controlled conditions and with appropriate endpoints could now be undertaken to test for an optimum dosage.

4.3. Vitamin D-related polymorphisms and mortality

The detrimental effects of low 25[OH]D serum levels have been studied in 33,996 European individuals. Variants at 3 loci had genome-wide significance for associations with 25[OH]D levels (4p12, 11q12, and 11p15). Subjects in the quartile with the highest genotype scores (combining 3 cited variants) had a higher risk of having 25[OH]D levels <75 nmol/L (odds ratio [OR] = 2.47) or <50 nmol/L (OR = 1.96) than those in the quartile with the lowest scores [45].

Fifty single nucleotide polymorphisms (SNPs) related to 25[OH]D concentrations were studied in Hispanic Americans [46]. Although three SNPs were identified as being significantly associated with $1,25[OH]_2D$ levels, none was associated with 25[OH]D levels. Five SNPs for 25[OH]D and 8 for $1,25[OH]_2D$ were replicated in the entire sample [46].

Karohl et al. [47] have reported that genetic factors may influence serum 25[OH]D levels in middle-aged male twins living at different locations in the US. They suggested that 25[OH]D levels vary during winter but not summer months. The authors estimated that 70% of the vitamin D variations during winter are explained by genetic factors. Contrary to this, Snellman et al. [48] considered that 25[OH]D variability during the summer in twins of the same sex is due to genetic factors, whereas low serum levels seen during the winter are due to shared environmental factors. The authors stated that a quarter of the serum 25[OH]D variation is due to individual-specific environmental factors [48].

VDR polymorphisms have been associated with different diseases, which in turn may increase mortality rates; furthermore, such polymorphisms may partly explain some of the conflicting results discussed above. In particular, epidemiological studies have produced controversial results concerning the association between vitamin D status and cancer-related mortality. Raimondi et al. [49] reported a meta-analysis of the most studied VDR polymorphisms (FokI and BsmI) and cancer at any body site. A significant increase in skin and breast cancer risk was found with genotype Fokl ff compared with FF carriers. For the same genotype comparison, a significantly higher risk of cancer was found after pooling estimates from cancer sites possibly associated with vitamin D levels (prostate, breast, skin, ovary and colorectal, as well as non-Hodgkin lymphoma). Prostate cancer risk was significantly reduced for BsmI Bb carriers compared with individuals with the bb genotype.

Mortality association with the VDR polymorphism FokI, three haplotypes of the Cdx2 and GATA polymorphisms, and three haplotypes of the BsmI, ApaI, and TaqI polymorphisms was analyzed in a prospective cohort in the Longitudinal Aging Study Amsterdam, in which 923 individuals aged 65 years or more were followed-up for 10.7 years (median) [50]. The authors reported that homozygosity for the Cdx2-GATA haplotype 1 allele was associated with a mortality risk 30% higher than among individuals lacking the allele. This result was not influenced by 25[OH]D levels or cardiovascular risk factors.

Vitamin D status and VDR polymorphisms may be involved in preventing cancer progression and modifying cancer risk [51]. Certain VDR combined polymorphisms have been associated with a higher risk of prostate cancer progression. Individuals with BSM (B)–Apal (A)–Taql (t) were less likely to have high Gleason scores (more aggressive cancer) than were individuals with the combination BsmI (b) –ApaI (a) –TaqI (T), supporting the hypothesis that low levels of vitamin D increase prostate cancer progression [52]. Similar polymorphism combinations related to vitamin D (VDR, vitamin D binding globulin, hydroxylases) may contribute to potentiate the negative effects of low vitamin D levels in health and disease.

The apparently contradictory results regarding 25[OH]D serum levels and disease association discussed above, such as the U-shaped relationship (increased risk at both high and low concentrations), may reflect the presence of a mixture of genotype-defined subgroups. Combinations of vitamin D binding protein and VDR polymorphisms could explain such findings [53].

5. Frailty and vitamin D

Frailty is a multidimensional concept used to describe declining physical function and a vulnerability to psychological stress, including illness and hospitalization [54]. It includes 'shrinking' (i.e. sarcopenia), weakness, exhaustion, slowness and low physical activity. Frailty is a predictor of disability, falls, fractures and mortality. Numerous studies support the hypothesis that vitamin D deficiency impairs muscle function and therefore increases the risk of falls [7]. Low 25[OH]D levels have been linked to pain, sarcopenia, poor physical function and frailty [55–61], although the reports are inconsistent. An age-related decline in 25[OH]D levels appears earlier and faster in women than in men [62], which explains the higher rate of frailty in the former. Recent findings suggest that maintaining adequate levels of vitamin D in elders may reduce the risk of frailty [63–65].

In an older Dutch population (aged 65 years or more) within the Longitudinal Aging Study Amsterdam, low serum 25[OH]D levels were associated with a decline in current physical performance over 3 years. Physical performance was poorer among individuals with serum 25[OH]D levels <10 ng/mL and those with levels between 10 and 20 ng/mL, compared with those with levels above 30 ng/mL [66].

In a sample of non-institutionalized US residents, low 25[OH]D serum levels (<15 ng/mL) were associated with a 3.7-fold increase in the odds of frailty among whites and a 4.0-fold increase among non-whites. Ensrud et al. [65] analyzed data from women (aged 69 years or more) within the same American cohort and found that those with 25[OH]D serum levels between 20.0 and 29.9 ng/mL had the lowest risk of frailty, whereas this risk was higher among those with values below or above this range. Among non-frail women, lower baseline 25[OH]D levels were associated with a higher risk of frailty or death after 4.5 years. In an editorial accompanying that report, Rosen and Manson [67] emphasized that the results presented by Ensrud et al. [65] were consistent with previous observational studies and that the optimal 25[OH]D serum levels for preventing frailty would be between 20 and 30 ng/mL.

6. Confounding factors

Several potential confounding factors have been identified in observational and epidemiological studies. For instance, low 25[OH]D levels may actually be a marker of poor health, or poor health may result in reduced sun exposure and inappropriate diet and consequently lower 25[OH]D levels. Measurement error in recorded variables, changes in values after a single vitamin D baseline assessment, or unmeasured risk factors may confound findings. Publications that include individuals from the same cohort may produce unidentified bias by repeating analysis on the same population even when different selection criteria are used for the re-analysis. Finally, some studies have not taken into consideration all potential confounders; for example, including income in the regression model for the NHANES III cohort analysis resulted in a significant reduction in the cardiovascular mortality rate among

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blacks [22]. However, the confounding factors (potential and those not assessed) are not capable of explaining the negative effects of low vitamin D levels on longevity and mortality.

The "normal" vitamin D levels required for optimal cell functioning are still unknown. In addition, many epidemiological studies have not adjusted for health status, lifestyle and co-morbid conditions, and have measurement errors in recorded variables. Moreover, causes of death may be confounded or poorly specified and hence result in bias.

Regardless, low 25[OH]D levels do seem to be a marker of poor health. Low levels may result from reduced sun exposure (for example from a largely indoor lifestyle) and inadequate dietary intake, and are associated with low educational status.

7. The mechanisms of action of vitamin D

Longevity is a complex phenomenon related to biological and environmental factors. There is some evidence that vitamin D is involved in physiological processes that might be expected to underlie aspects of longevity, such as DNA repair, the prevention and repair of oxidative damage, and genetic immune regulation. Despite this, genotype differences in five VDR polymorphisms in octogenarians as compared with young controls did not reach statistical significance [68]. Thus, while vitamin D mediated protection against aging seems reasonable, the data supporting such a notion have come mostly from observational and epidemiological studies which have included different populations, used different methods and examined uncontrolled health variables, or that otherwise featured confounding factors.

Low vitamin D status may be considered an endocrine insufficiency but also a nutritional deficiency. Both would impair optimal health and genomic function. The current challenge is to find an optimal vitamin D level or range that would increase longevity and reduce morbidity. Some dietary components may improve human physiology and reduce health risks [69–71]. There is a need to study new mechanisms of action for vitamin D in order to explain the basis of its beneficial effects and aid in defining optimal vitamin D levels. The actions of vitamin D depend on 1-α-hydroxylase activity, VDRs, immune changes, genomic/non-genomic actions and antiproliferative and antioxidative effects [72,73].

7.1. The cardiovascular system

Low vitamin D status has been associated with CVD and related complications, and is an independent mortality risk factor [9,44,74]. PTH is crucial for calcium homeostasis and maintains a feedback with vitamin D levels. Some studies have demonstrated that elevated serum PTH (≥63 ng/mL) is an independent risk factor for death in elderly individuals [75,76]. Elevated serum PTH levels have also been associated with a decline in cognition, regardless of blood calcium balance and renal function [77]. This hyperparathyroidism is mostly caused by prolonged vitamin D deficiency.

PTH controls calcium homeostasis through specific receptors. These PTH receptors are present in the cardiovascular system, within both vessel walls and the myocardium. Several studies have demonstrated an association between high PTH levels and hypertension, myocardial dysfunction and vascular disease [78–83]. In addition, hyperparathyroidism is also associated with increased mortality [83–85].

It seems likely that low vitamin D levels may precede the development of cardiovascular conditions such as hypertension, insulin resistance and diabetes. Vitamin D deficiency may affect the vascular endothelium and the renin–angiotensin system, whereas its effects on vascular smooth muscle may induce cell proliferation, inflammation and thrombosis [86].

7.2. The immune system

Hormones and immune function decay have been implicated in aging. Low levels of different hormones and immune senescence conjointly alter cell functions. Nevertheless, the organization of and interactions between hormones and the immune system remain unclear [87]. Insulin growth factor secretion, adrenal dehydroepiandrosterone and tissue-specific availability of vitamin D are all potentially involved in aging. In general, the aging process is associated with reduced protein synthesis, reductions in lean body tissue and bone mass, fat mass increase, insulin resistance, fatigue, depression, anemia, decreased libido and an increase in degenerative conditions and cancer [88].

Leukocyte subsets have VDRs, which suggests that vitamin D has a direct effect on these cells [89,90]. This may explain, in part, connections between vitamin D and autoimmune disease. Helper T (Th) cells are pivotal to antigen-specific immune responses. Naive Th cells develop into 2 subtypes (Th1 or Th2) according to the microenvironment. A normal immune response depends on a balance of the 2 subtypes [91–93]. Th1 cells are pivotal for cell-mediated immune responses, including reactions to tumors and intracellular pathogens (such as viruses). T cells attack and destroy all cells with traces of foreign pathogens (bacteria and viruses) through appropriate signaling to the immune system. This mechanism guarantees that the system will produce a more efficient and enhanced immune response.

Vitamin D has specific actions on the immune system (particularly T lymphocytes) and the regulation of several cytokines (secretion and actions). It regulates immune responses by suppressing T cell proliferation and modulating macrophage function [94]. In mice, vitamin D prevents the induction of autoimmune diseases as well as T helper subset responses. $1,25[OH]_2D$ inhibits T monocyte and B cell interleukin 12 secretion, which in turn leads to Th1 activation and differentiation. In addition, 1,25-(OH)2-D3 directly inhibits interferon-gamma secretion by Th1 clones [95].

T cell activation is also under vitamin D regulation. The concentrations of intracellular 25[OH]D and $1,25[OH]_2D$ in isolated T cells are similar to those found in serum. Hence, deficient levels in serum may reflect a severely compromised immune system [96,97]. In recent years vitamin D deficiency has been associated with different autoimmune diseases, including insulin-dependent diabetes mellitus, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus and rheumatoid arthritis [98,99].

7.3. Oxidative stress

Aging and several chronic diseases (cancer and atherosclerosis) have been associated with oxidative stress: that is, increased free radical formation and/or decreased antioxidant levels [100,101]. Vitamin D deficiency causes endothelial dysfunction, and may thereby contribute to atherosclerosis and cancer.

Bao et al. [102] have reported the protective role of $1,25[OH]_2D$ against oxidative stress in non-malignant human prostate epithelial cells. Protection from cellular injuries induced by reactive oxygen species is via transcriptional activation of the antioxidant glucose-6-phosphate dehydrogenase. Cancer cells do not display similar activity.

Endothelial function as measured by flow-mediated dilatation of the right brachial artery is significantly lower in subjects with 25[OH]D levels <25 nmol/L, compared with sex-matched controls with mean 25[OH]D values of 75 nmol/L. Endothelial function increased after vitamin D treatment [103]. These results fit well with other reports that vitamin D insufficiency is associated with atherosclerosis.

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7.4. Antiproliferative effects of vitamin D

Vitamin D exerts several antiproliferative actions through direct genomic action and by other mechanisms, including cell stress protection, cytotoxic action, apoptosis and angiogenesis inhibition. In addition, 1,25[OH]$_2$D may potentiate the effects of many cytotoxic and antiproliferative anticancer agents [104,105].

There is both experimental and clinical evidence that vitamin D has some carcinogenic activity, including regulation of cell growth and differentiation, apoptosis, cytotoxic and antiangiogenic effects [106–108]. VDR knock-out mice display increased mammary gland tumorigenesis and chemical-induced carcinogenesis. This suggests that vitamin D is involved in tumor development [109,110]. High doses of calcitriol and novel vitamin D analogues have demonstrated cytotoxic effects over cancer cells, angiogenesis inhibition, and chemotherapy potentiation under experimental conditions. This opens new scenarios for future research and the development of new management options.

7.5. Telomere attrition

The telomere is the genetic material that caps the free end of cell DNA. With aging, the telomere shortens and DNA becomes increasingly unstable, until eventually the cell dies. Leukocyte telomere length (LTL) is a marker of age-related disease, decreasing with each cycle and inflammation. LTL is considered a biomarker of overall well-being and a predictor of disability among older individuals. LTL has been associated with disability, hypertension, CVD, diabetes, cancer and oxidative stress [111,112]. Richards et al. [113] studied telomere length and serum 25[OH]D levels in 2160 women aged 18–79 (mean 49.4 years) from a large population-based cohort of twins. An inverse association between LTL and serum 25[OH]D levels was found. Thus, LTL was 107 base pairs more (equivalent to 5 years of normal aging) in individuals in the upper vitamin D tertile compared with those in the lowest tertile. This difference was associated with increased C-reactive protein levels, a marker of systemic inflammation.

8. Final remarks

Many people have chronically low levels of endogenous vitamin D. Rickets and osteomalacia are common even in countries where foodstuffs are fortified with vitamin D. Although the evidence is somewhat controversial, it seems that mortality may be related to sustained hypovitaminosis D, a situation that is easily corrected. There is no consensus on what constitutes 'normal' vitamin D levels. Many scientists have considered 30 ng/mL as an optimal level, whereas others suggest 40 ng/mL especially when conditions such as cancer are involved [114,115]. Appropriate lifestyle changes, such as regular short exposures to sunlight (15–20 min a day), are not always easily accomplished. Vitamin D supplementation should therefore be performed, with dosages higher than those traditionally suggested [3,116].

The Institute of Medicine of the US National Academies has recommended an increase in vitamin D minimal daily requirements and at the same time has increased its estimate of an upper limit on a safe dose to 4000 IU/day of vitamin D. New clinical trials should be designed with these higher limits. An increase in calcium doses has not been recommended. The American Dietary Reference Intake (DRI) for vitamin D is intended as a guideline for the general population [117]. It does not take into consideration medical history, individual risks, clinical symptoms, environmental conditions or nutritional assessment.

The emerging evidence associating high vitamin D levels with longevity deserves to be explored through prospective controlled studies. Clinical trials are needed to determine whether adequate supplementation may neutralize the supposed negative effects of prolonged low vitamin D status. The ongoing Vitamin D and Omega-3 Trial (VITAL) [118] will provide some answers to the many questions and is expected to confirm the benefits of vitamin D. The trial will run for five years and include women (≥65 years) and men (≥60 years) randomized to one of four groups: daily vitamin D (2000 IU) and fish oil (1 g); daily vitamin D and fish-oil placebo; daily vitamin-D placebo and fish oil; or daily vitamin-D placebo and fish-oil placebo.

Grant et al. [114] have calculated the direct and indirect costs of increasing mean serum 25[OH]D levels through the daily vitamin D intake of 2000 to 3000 IU/day. The authors estimated that this measure would annually save 187,000 million euros, whereas the cost of the strategy (vitamin D supplementation, educational program and tests) would be 10,000 million euros/year. These interventions, however, require more scientific support and supranational coordination. Estimation models have been developed in European Nordic countries [115] to determine the health impact of increasing 25[OH]D levels through oral vitamin D intake and ultraviolet B irradiance. It has been estimated that by increasing serum 25[OH]D to 105 nmol/L, the possible mortality reduction would be 11% in Denmark, 17% in Finland, 24% in Iceland, 18% in Norway, and 18% in Sweden. Grant et al. [119] have also calculated the theoretical benefit of increasing in Canada mean 25[OH]D serum levels to 105 nmol/L; their estimate was of 37,000 fewer deaths per year.

In light of the fact that billions of human beings have blood vitamin D levels in a range that would be deemed to represent either insufficiency or manifest deficiency, the vitamin D system is an important subject of study. However, the benefits of vitamin D treatment are still under evaluation. It seems reasonable to maintain an optimal vitamin D status to guarantee the actions of this compound over the more than 150 identified genes. There is a growing interest in the mechanisms of aging and longevity, as interventions in the aging process may allow specific diseases to be treated or prevented. Furthermore, the identification of anti-aging factors should ultimately allow healthcare expenditures to be reduced.

Provenance and peer review

Commissioned and externally peer reviewed.

Contributors

Faustino R. Pérez-López contributed to the study design, searched the literature, and formatting and editing the initial and final version of the paper. Peter Chedraui contributed to the study providing intellectual input and formatting of the final document. Ana M. Fernández-Alonso contributed to the study providing intellectual input and formatting of the final document.

Competing interests

The authors report no conflicts of interest.

Funding

The authors disclosed receipt of the following financial support for the research and authorship of this article: B/024535/09 AECID ("*Agencia Española de Cooperación Internacional para el Desarrollo*") grant from the Spanish "*Ministerio de Asuntos Exteriores y Cooperación*".

Please cite this article in press as: Pérez-López FR, et al. Vitamin D and aging: Beyond calcium and bone metabolism. Maturitas (2011), doi:10.1016/j.maturitas.2011.02.014

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Please cite this article in press as: Pérez-López FR, et al. Vitamin D and aging: Beyond calcium and bone metabolism. Maturitas (2011), doi:10.1016/j.maturitas.2011.02.014