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Changes in vitamin D endocrinology during aging in adults

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Invited review for the Special issue in Molecular and Cellular Endocrinology “Endocrine function of vitamin D”

Title: Changes in vitamin D endocrinology during aging in adults.

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; 1,25(OH)2D, 1,25dihydroxyvitamin D; 24,25(OH)2D, 24,25-dihydroxyvitamin D; CYP2R1, 25-hydroxylase; CYP27B1, 1alpha-hydroxylase; CYP24A1, 24-hydroxylase; VDR, vitamin D receptor; FGF-23, fibroblast growth factor 23.

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1 Abstract (max 150 words)

2 Worldwide, vitamin D deficiency is a common finding. Within individuals 25-hydroxyvitamin D  
3 (25OH)D concentrations remain fairly stable over time although large differences in individual  
4 longitudinal changes exist. During aging vitamin D metabolism and activity changes in several  
5 different ways. Intestinal resistance to 1,25(OH)2D develops which hampers intestinal calcium  
6 uptake. Vitamin D receptor number decreases with aging in several organs involved in calcium  
7 metabolism and 1 $\alpha$ -hydroxylase activity decreases mainly due to a decrease in renal function  
8 reducing vitamin D activation. Effects of 1,25(OH)2D on cell proliferation and differentiation may  
9 influence potential anti-cancer effects whereas regulation of telomere length may result in longevity.  
10 In older individuals, vitamin D supplementation has positive effects on fracture risk, number of falls  
11 and physical function. Supplementation in older populations warrants specific attention. Effects on  
12 “non-classical” outcomes may be revealed by ongoing large randomized clinical trials with high doses  
13 of vitamin D.

14

15 Keywords (max 6)

16 25-hydroxyvitamin D; 1,25-dihydroxyvitamin D; aging; vitamin D receptor; telomere

Highlights: 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

- 1 • Vitamin D deficiency is very common worldwide
- 2 • Aging in humans results in less metabolic activity of vitamin D.
- 3 • Aging leads to a decrease in vitamin D receptor number in several organs
- 4 • Vitamin D may influence cellular aging through effects on telomere biology.

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1. Introduction
2. Prevalence of vitamin D deficiency
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4. Vitamin D metabolism and action during aging
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## 1 1. Introduction

2 Vitamin D is primarily produced in the skin under the influence of UV-B light of the sun on 7-  
3 dehydrocholesterol. In most adult individuals, dietary intake of vitamin D, from sources such as fatty  
4 fish, provides only a small additional contribution to vitamin D status. In older individuals, dietary  
5 intake becomes more important. Vitamin D requires two hydroxylation steps to become fully  
6 activated. The first step occurs in the liver by 25-hydroxylase (CYP2R1), which produces 25-  
7 hydroxyvitamin D (25(OH)D). The second step involves hydroxylation by 1 alpha-hydroxylase  
8 (CYP27B1) to 1,25-dihydroxyvitamin D (1,25(OH)<sub>2</sub>D) mainly in the kidney. 25(OH)D is the  
9 predominant circulating form of vitamin D mostly bound to vitamin D binding protein. 25(OH)D has a  
10 long half-life in contrast to 1,25(OH)<sub>2</sub>D and is generally considered the best marker of vitamin D  
11 status. When 1,25(OH)<sub>2</sub>D is sufficiently present, 24,25-dihydroxyvitamin D (24,25(OH)<sub>2</sub>D) is formed  
12 in the kidney by 24-hydroxylase (CYP24A1) and further catabolized. A number of extra-renal tissues  
13 are able to convert 25(OH)D to 1,25(OH)<sub>2</sub>D. The 1,25(OH)<sub>2</sub>D produced by these tissues appears to  
14 act locally in an autocrine or paracrine fashion and does not contribute significantly to the circulating  
15 1,25(OH)<sub>2</sub>D concentrations (1).

16  
17 Vitamin D exerts its effects on the one hand through genomic effects by binding to the nuclear  
18 vitamin D receptor (VDR) and vitamin D responsive elements of many genes and on the other hand  
19 through rapid non-genomic effects through a postulated membrane receptor and second  
20 messengers (2). VDR is present throughout the body in many different cell types such as immune,  
21 muscle and bone cells. Vitamin D is essential for the efficient intestinal absorption of calcium and  
22 phosphate to create sufficient local concentrations of calcium and phosphate for adequate bone  
23 mineralization. Vitamin D in children has mainly been recognized for its important role in bone  
24 health. A deficiency of 25(OH)D in children may result in the clinical picture of rickets in which  
25 defective mineralization or calcification of bones before epiphyseal closure leads to fractures and  
26 deformities. Inadequate mineralization of bone at adult and older age results in osteomalacia and is

1 often the result of deficient concentrations of 25(OH)D. Low concentrations of 25(OH)D also  
2 contribute to the development of osteopenia and osteoporosis through an increase in parathyroid  
3 hormone concentrations and an increase in bone turnover (1,3). Vitamin D deficiency also predicts  
4 functional decline and sarcopenia at older age (4,5). Through these mechanisms 25(OH)D is a  
5 determinant of falls and fractures in older populations. Last decades, vitamin D deficiency has been  
6 associated with a wide spectrum of age-related diseases such as diabetes mellitus type 2,  
7 cardiovascular disease and cancer, in particular in older individuals (6). Causality for these so-called  
8 “non-classical” outcomes, however, remains to be established. The clinical consequences of  
9 deficient 25(OH)D concentrations warrant a sufficient level at all ages. Special attention may be given  
10 to 25(OH)D concentrations in older individuals because they are characterized, amongst others, by a  
11 high prevalence of falls and fractures.

12 In the present review we aim to present an overview of different factors contributing to changes in  
13 vitamin D endocrinology during the aging process. Hereby we will focus on the human adult. We will  
14 go further into the potential role of vitamin D in cellular aging and telomere biology. Finally, we will  
15 discuss the potential consequences of these changes on human health and disease.

## 1    2.    Prevalence and risk factors of vitamin D deficiency.

2    The formation of active 1,25(OH)<sub>2</sub>D by 1-alpha hydroxylase is dependent on sufficient availability of  
3    the substrate 25(OH)D. The prevalence of 25(OH)D concentrations below 50 nmol/L is still a  
4    widespread problem worldwide (7-10). Vitamin D deficiency affects all age groups, from the newborn  
5    to the older adult, and is dependent on several lifestyle and environmental conditions. Specific risk  
6    groups for vitamin D deficiency are young children, pregnant women, older persons in particular  
7    institutionalized and home-bound individuals, and non-western immigrants. In Southeast Asia and  
8    Mongolia more than 90% of children and the young adult population has vitamin D deficiency. In the  
9    U.S. and Europe the percentage of older adults still living in the community having deficient 25(OH)D  
10    concentrations is also high and ranges from 20 to 100% (7,12). In institutionalized and home-bound  
11    individuals the prevalence of vitamin D deficiency is even higher (13,14). In general, older age, female  
12    sex, higher latitude, winter season, darker skin pigmentation, less sunlight exposure, low intake of  
13    vitamin D containing food, and absence of vitamin D fortification are the main factors that are  
14    associated with lower 25(OH)D concentrations worldwide (7-10).

15            Many factors potentially contribute to the presence of vitamin D deficiency at any age (Table  
16    1). During the aging process, however, the contribution of these risk factors to the presence of low  
17    25(OH)D concentrations changes (11). As the general population ages the relative amount of women  
18    compared to men increases. Most studies demonstrate that older women are more prone to be  
19    25(OH)D deficient than older men (8,10).

20            In the skin, previtamin D is produced by exposure of 7-dehydrocholesterol to ultraviolet (UV)  
21    radiation. Older individuals spent less time outdoors particularly if they are institutionalized or home-  
22    bound. In addition, the amount of 7-dehydrocholesterol in skin cells decreases as the body ages  
23    which in turn decreases the capacity to synthesize previtamin D (16). Nevertheless, exposure to UV  
24    irradiation in older nursing-home residents is capable to increase 25(OH)D concentrations to the  
25    normal range with doses less than those required to produce erythema (17,18).

1 Table 1. Risk factors for vitamin D deficiency

Female gender	
Pregnancy	
Reduced sunlight exposure	Less time spent outdoors, reduced mobility, more use of sunscreen, protective clothing
Low ambient UV radiation level	High latitude location, winter season
Dark skin pigmentation	
Reduced nutritional intake	Restricted diet, no supplement use, no use of food fortification
Malabsorption syndromes	Eg. short bowel syndrome, cystic fibrosis, celiac disease
Obesity	
Medications	Eg. anticonvulsants, glucocorticoids, loop diuretics and statins

2

3 In addition to sunlight-related factors, intake of vitamin D may change during aging. Dietary intake of  
4 vitamin D is generally low in all age groups and is unlikely to exceed 400 IU daily unless there is a lot  
5 of fish with high vitamin D content in the diet such as in some Scandinavian countries. Also, dietary  
6 intake is highly dependent on food fortification with vitamin D which occurs in the United States,  
7 Canada and some European countries including Finland and Sweden. In the United States an increase  
8 in total vitamin D intake was shown after the age of 50 years. This was caused by a higher amount of  
9 vitamin D supplementation use (11)

10 As adults age body composition changes towards more fat and less muscle mass. The amount of  
11 adipose tissue is inversely related to 25(OH)D concentrations (12). Several mechanisms are  
12 hypothesized to contribute to this inverse relationship such as sequestration of vitamin D in adipose  
13 tissue, increased catabolism of vitamin D due to local CYP24A1 in adipose tissue or diminished  
14 synthesis of 25(OH)D by the liver enzyme CYP2R1 (13) in the presence of hepatic fat. Increased use  
15 of medications as often occurs during aging also influences 25(OH)D concentrations (14,15). Some  
16 drugs such as anticonvulsants and rifampicin activate the nuclear steroid xenobiotic receptor which

- 1 interacts with the VDR and probably regulates enzymes responsible for 1,25(OH)<sub>2</sub>D production and
- 2 degradation (16). Other drugs have also been shown to be related to lower 25(OH)D concentrations,
- 3 for example loop diuretics, glucocorticoids and statins although causality and clinical relevance may
- 4 be doubtful in these relationships (14,15).

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### 1 3. Longitudinal changes in 25-hydroxyvitamin D concentrations during aging

2 To our knowledge, only four studies examined the longitudinal change in 25(OH)D concentrations  
3 within individuals over several years (i.e. aging effect) (17-20). In general, all four studies  
4 demonstrate that 25(OH)D concentrations remain fairly stable over time with on average, larger  
5 seasonal variation than longitudinal change. In the Dutch Longitudinal Aging Study Amsterdam it was  
6 shown that 25(OH)D concentrations increased with 4 nmol/L in individuals aged 55–65 years old  
7 during a period of 6 years. In contrast, serum 25(OH)D levels decreased with 4 nmol/L in persons  
8 aged 65–88 years old during a period of 13 years (17). In the Tromsø Study age was not a significant  
9 predictor of 25(OH)D concentrations. Nevertheless, it was reported that individuals older than 65  
10 years had a decrease in serum 25-OHD levels of 0.3 nmol/L, and subjects younger than 65 years had  
11 an increase in serum 25-OHD levels of 2.0 nmol/L during 14 years of follow-up (18). Among US blacks  
12 and whites, it was demonstrated that mean 25(OH)D levels also did not change during 14 years of  
13 follow-up although there was a high individual variation. Increases in 25(OH)D concentration over  
14 time were associated with male gender, use of vitamin D supplements, greater physical activity, and  
15 higher high-density lipoprotein-cholesterol. Decreases in 25(OH)D levels over time were associated  
16 with current smoking, higher body mass index, higher education, diabetes, and hypertension (19). In  
17 a population-based Canadian cohort, 25(OH)D concentrations increased over 10 years in all age  
18 groups and in both sexes but especially in women. The measured increase in use of vitamin D  
19 supplements did explain a large part but not the total increase in 25(OH)D concentrations over time  
20 (20). To our knowledge, longitudinal changes within individuals in 1,25(OH)<sub>2</sub>D concentrations are  
21 not reported in the literature. Cross-sectional analyses demonstrate a lower 1,25(OH)<sub>2</sub>D  
22 concentration in the older as compared to the younger adults (21).

23 To conclude, in general longitudinal 25(OH)D concentrations remain fairly stable over time,  
24 although there may be an indication that concentrations decline in the older old individuals as  
25 compared to middle-aged adults. A causal role of age-related changes in vitamin D metabolism

- 1 therein remains to be proven. Longitudinal changes are largely influenced by changes in lifestyle and
- 2 other factors related to vitamin D deficiency including the use of vitamin D supplements.

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#### 1 **4. Vitamin D metabolism and action during aging**

2 During aging vitamin D metabolism changes in several ways in different organs, which we will  
3 describe below. The potential age-related changes in vitamin D metabolism and activity are depicted  
4 in Figure 1.

##### 5 **4.1 Intestinal calcium absorption**

6 The most important role of 1,25(OH)<sub>2</sub>D is stimulation of intestinal calcium and phosphate  
7 absorption. Calcium absorption is fairly stable during adulthood but starts to decline at  
8 approximately the age of 60 years (22,23). One of the factors contributing to this decrease in calcium  
9 absorption may be the development of intestinal resistance to 1,25(OH)<sub>2</sub>D. A study in women  
10 demonstrated a close relationship between serum 1,25(OH)<sub>2</sub>D and fractional calcium absorption in  
11 young women (28±5 years) whereas this relationship was absent in old women (73±3 years)(24). Rat  
12 studies have supported the development of intestinal resistance to 1,25(OH)<sub>2</sub>D during aging (25).  
13 The contribution of a decrease in VDR to this 1,25(OH)<sub>2</sub>D resistance in the aging intestine remains  
14 controversial. Some studies support a reduction in intestinal VDR with age in humans (26) whereas  
15 others do not (27). It is also possible that the age-related resistance of the intestine to 1,25(OH)<sub>2</sub>D  
16 may be due, at least in part, to a post-receptor defect in 1,25(OH)<sub>2</sub>D action. For example, part of the  
17 change in calcium absorption with aging may be because of abnormalities in the transport proteins  
18 that are regulated by 1,25(OH)<sub>2</sub>D such as the calcium-binding protein calbindin-D9k and the  
19 epithelial calcium channel transient receptor potential vanilloid type 6 (TRPV6) (28).

##### 20 **4.2 Renal production of active vitamin D and calcium reabsorption**

21 The kidney is an important player in the regulation of the amount of active 1,25(OH)<sub>2</sub>D available.  
22 With aging, there is a decrease in renal production of 1,25(OH)<sub>2</sub>D by the kidney associated with the  
23 decline in renal function (29,30). Studies in rats show that CYP27B1 activity decreases and CYP24A1  
24 activity increases with aging leading to less availability of 1,25(OH)<sub>2</sub>D (31,32). Animal studies have

1 also shown that the stimulatory effect of PTH or low phosphate diet on CYP27B1 expression is  
2 blunted in older rats as compared to younger ones (33,34). In women, the effect of parathyroid  
3 hormone (hPTH[1–34]) infusion on serum 1,25(OH)<sub>2</sub>D and calcium absorption decreased with age,  
4 also suggesting the development of renal PTH resistance (30,35). Recent studies have suggested that  
5 increased FGF23 may be the initial event leading to the suppression of 1,25(OH)<sub>2</sub>D synthesis that is  
6 associated with functional deterioration of the kidney (36). 1,25(OH)<sub>2</sub>D can induce the expression of  
7 both FGF23 and its co-receptor klotho whereas FGF23 can suppress renal expression of CYP27B1 to  
8 reduce 1,25(OH)<sub>2</sub>D activity (37). Coincident with the decline in renal production of 1,25(OH)<sub>2</sub>D ,  
9 there is also an age-related decrease in renal VDR and TRPV5 expression, which is accompanied by  
10 lower renal calcium reabsorption efficacy (38).

#### 11 **4.3 Metabolism and activity of vitamin D in the musculoskeletal system**

12 Vitamin D deficiency contributes to the development of osteoporosis and sarcopenia in older  
13 individuals which increases the risk of fractures and falls and concomitant morbidity and mortality.  
14 Indeed, vitamin D status predicts osteoporotic fracture risk, loss of muscle mass and functional  
15 decline in older individuals (3-5).

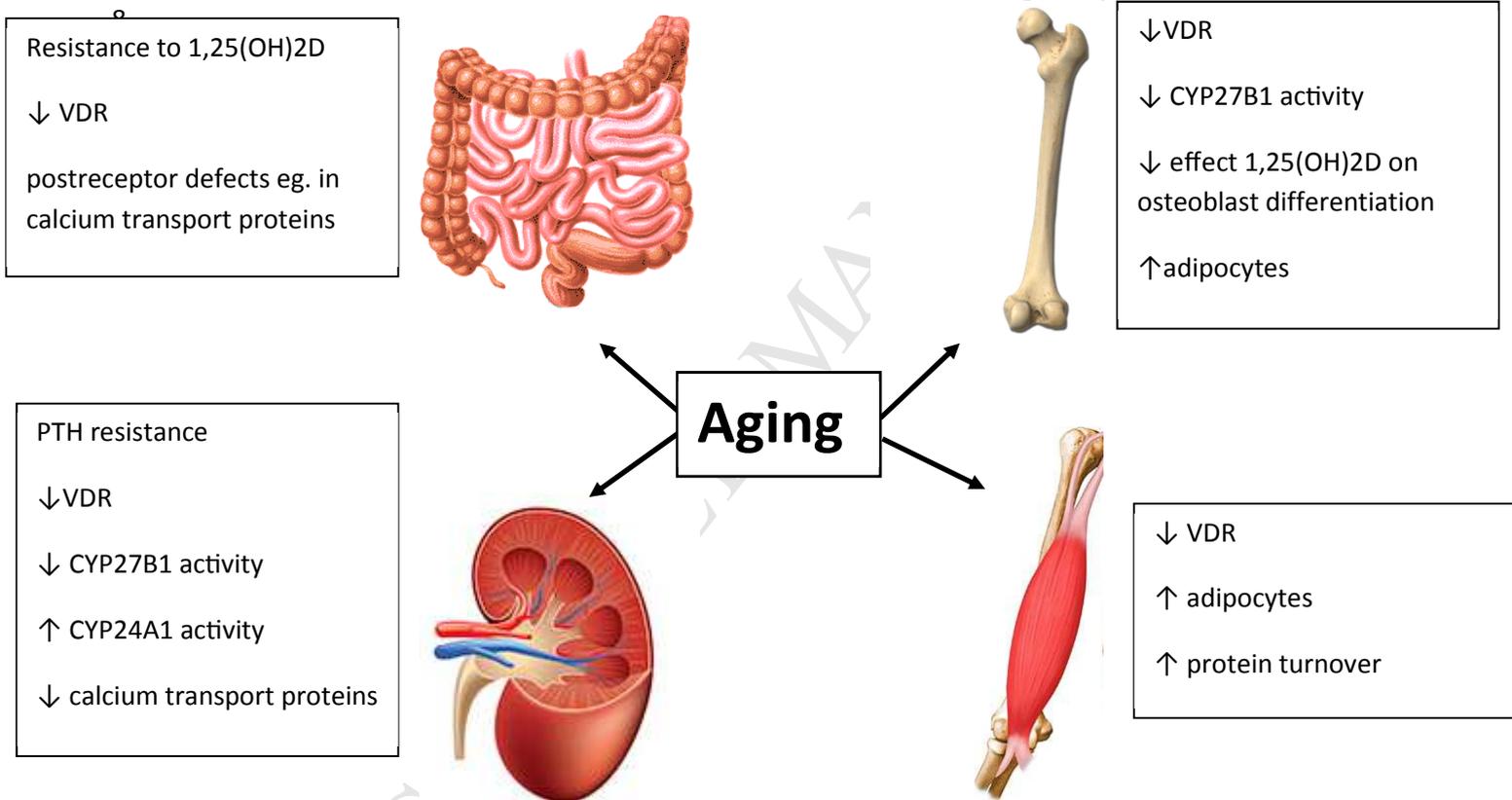
16 With increasing age, PTH concentrations increase both due to the high prevalence of vitamin D  
17 deficiency as well as due to decreased kidney function. The increase in PTH concentrations  
18 contributes to mainly cortical bone loss and increased prevalence of osteoporosis. 1,25(OH)<sub>2</sub>D has  
19 also been shown to directly influence bone metabolism. 1,25(OH)<sub>2</sub>D is locally produced in bone by  
20 CYP27B1 activity of bone cells. VDR is present on osteoblasts, osteocytes and osteoclasts implicating  
21 a paracrine and autocrine activity. 1,25(OH)<sub>2</sub>D has the potential to stimulate osteoclastic bone  
22 resorption, enhance osteoblast differentiation and promote mineralization (39,40). In this way,  
23 1,25(OH)<sub>2</sub>D is capable to influence both anabolic and catabolic bone processes. The regulation of  
24 these effects is not completely understood but probably dependent on calcium homeostasis (39).

1 Both in bone and muscle, VDR expression decreases with aging contributing to less 1,25(OH)<sub>2</sub>D  
2 activity in the musculoskeletal system (41,42). Also, in bone cells CYP27B1 concentrations  
3 demonstrate an age-dependent decrease and 1,25(OH)<sub>2</sub>D-stimulated osteoblast differentiation is  
4 hampered when osteoblasts are derived from aged as compared to young individuals (43). In muscle,  
5 vitamin D deficiency activates pathways which lead to increased protein turnover and consequently  
6 muscle atrophy (44). Finally, both increasing age and vitamin D deficiency are related to increased  
7 infiltration of both bone and muscle with adipocytes. In vitro studies demonstrate that this process  
8 may be reversed by active vitamin D. In muscle cells, a high 1,25(OH)<sub>2</sub>D dose inhibits the formation  
9 of lipid droplets (45). Similarly, in bone, 1,25(OH)<sub>2</sub>D inhibited bone marrow adipogenesis and  
10 stimulated osteogenesis (46). Whether these processes also play a role in vivo in humans remains to  
11 be demonstrated.

#### 12 **4.4. Substrate deficiency**

13 In older individuals, vitamin D deficiency is a common finding . The lack of the substrate 25(OH)D for  
14 the formation of 1,25(OH)<sub>2</sub>D may contribute to decreased calcium absorption and other actions of  
15 1,25(OH)<sub>2</sub>D. However, previous human studies have suggested that the serum 25(OH)D  
16 concentration is not critical for serum 1,25(OH)<sub>2</sub>D formation until the serum 25(OH)D falls below  
17 approximately 10 nmol/L (47). Less severe vitamin D deficiency, nevertheless, is deleterious to bone  
18 because it is associated with secondary hyperparathyroidism. Reduced calcium absorption due to  
19 vitamin D deficiency results in increased parathyroid hormone secretion to maintain calcium  
20 homeostasis. PTH is capable of binding directly to osteoblasts. PTH stimulates the expression of the  
21 receptor activator of nuclear factor kappa B ligand (RANKL) and inhibits the secretion of  
22 osteoprotegerin (OPG), a soluble decoy receptor of RANKL. The binding of RANKL to RANK (facilitated  
23 by the decreased amount of OPG available for binding the excess RANKL) stimulates these osteoclast  
24 precursors to form new osteoclasts, which ultimately enhances bone resorption.

- 1 The role of 1,25(OH)<sub>2</sub>D, however, seems to be limited in the age-related changes in intestinal calcium  
 2 absorption. The correlation between serum 1,25(OH)<sub>2</sub>D and calcium absorption tests only accounts  
 3 for 12-30% of the variance in the age-related change in the calcium absorption tests (19). Therefore,  
 4 other factors than availability of 1,25(OH)<sub>2</sub>D as mentioned above are more likely to contribute.
- 5 Figure 1. Mechanisms contributing to changes in vitamin D endocrinology during aging confined to  
 6 the intestine, kidney, bone and muscle. 1,25(OH)<sub>2</sub>D, 1,25-dihydroxyvitamin D; VDR, vitamin D  
 7 receptor; FGF23, fibroblast growth factor-23.



## 1 5. Vitamin D, cellular aging and telomere biology

2 In vitro studies have shown a direct regulatory effect of the active vitamin D metabolite on proteins  
3 that play a role in the cell cycle such as cyclins and cyclin-dependent kinases (48). Active vitamin D  
4 can result in cell cycle arrest by for example down-regulating c-myc, a master regulator of cell  
5 proliferation (49). In addition, 1,25(OH)<sub>2</sub>D can influence cell proliferation through indirect pathways.  
6 For example, vitamin D inhibits the NF-κB pathway (50). The transcription factor NF-κB is an  
7 important regulator of cellular responses to inflammation, stress or injury and is chronically activated  
8 in many age-related disorders such as cardiovascular disease, type 2 diabetes mellitus or  
9 osteoporosis (48). Also, the suppression of proliferation and stimulation of differentiation of cells by  
10 1,25(OH)<sub>2</sub>D may play a role in potential anti-cancer effects. Another mechanism by which vitamin D  
11 may influence cellular aging is FGF23 and Klotho production (51). Defects of FGF23 and Klotho  
12 expression in animal studies lead to premature aging phenotypes. However, the underlying  
13 mechanism of these effects of the FGF23-Klotho axis are currently still unknown.

14 Another pathway through which vitamin D can influence cellular aging is through effects on telomere  
15 biology. Telomeres are repetitive DNA sequences that protect the ends of linear chromosomes. With  
16 increasing age telomeres of human tissue cells and stem cells shorten because the amount of  
17 telomerase present is insufficient to maintain telomere length during repetitive cell division. In  
18 addition, telomere shortening is accelerated by oxidative stress, inflammation, and cell proliferation  
19 (48). Shorter telomeres in leukocytes have been found to be associated with increased incidence of  
20 chronic diseases, such as type 2 diabetes mellitus, cardiovascular disease and cancer, although  
21 causality in these associations is still a matter of debate(52). The same accounts for vitamin D  
22 deficiency demonstrating associations with multiple outcomes without convincing evidence of  
23 causality (53). Considering the role of 1,25(OH)<sub>2</sub>D in inflammation and cell differentiation, it has  
24 been postulated that a deficiency contributes to telomere shortening and results in genomic  
25 instability. In recent human studies, an association between higher concentrations of 25(OH)D and

1 longer leukocyte telomere length was present in pre- and postmenopausal women (54,55), but this  
2 finding could recently not be reproduced in young adulthood (56). In addition, small longitudinal and  
3 intervention trials that have been performed in highly specific populations support a potential  
4 positive effect of vitamin D supplementation on telomere length but have too many limitations to  
5 draw definitive conclusions (48). Positive effects on telomere length may lead to genetic integrity and  
6 stability which may ultimately result in longevity. Large randomized controlled trials will hopefully  
7 lead to the definite answer regarding vitamin D effects on telomere biology. Currently, large  
8 randomized clinical trials with high doses of vitamin D (2000-3000 IU/d) are going on with multiple  
9 endpoints and these may provide the answer.

## 1    **6. Prevention and treatment of vitamin D deficiency**

2    Prevention of vitamin D deficiency in older individuals should start with changes in modifiable risk  
3    factors, including limited unprotected sun light exposure, weight loss, adjustment in drugs used and  
4    an increase in nutritional intake of vitamin D. Beside these measures, older individuals should be  
5    advised to take vitamin D supplementation. Vitamin D supplementation is cheap, safe if used in the  
6    right dosage and easy to apply. Previous trials demonstrate positive effects of moderate dose vitamin  
7    D supplementation on fracture risk (together with calcium supplementation), number of falls and  
8    physical function in older individuals (57-59). Therefore, many guidelines advise moderate dose  
9    vitamin D supplementation for older adults to maintain bone health and to prevent falls. For  
10    example, the Institute of Medicine recommends 600 IU (15 ug) of vitamin D daily for all ages up to  
11    age 70 and 800 IU (20 ug) after age 71 (60). The International Osteoporosis foundation advises 800-  
12    1000IU (20-25ug) for all individuals aged 65 years and older (61). The guidelines acknowledge that  
13    higher dosages of up to 2000 IU (50ug) daily may be warranted in case of older individuals with  
14    specific risk factors such as the presence of obesity, osteoporosis, limited sun exposure (e.g.  
15    institutionalized and home-bound) or malabsorption. However, caution should be taken with very  
16    high supplementation dosages (> 50.000 IU colecalciferol per month) because three previous trials  
17    have demonstrated increased fall risk with these supplementation dosages (62-64). The mechanism  
18    underlying this increased fall risk remains unclear but may be related to the high peak 25(OH)D  
19    concentrations reached. Unfortunately, in daily practice, implementation of the guidelines remains  
20    troublesome. For example, in the Netherlands, vitamin D supplement use is restricted to only 10 to  
21    25% of the older population (65). Therefore, particularly in older populations, much attention for  
22    prevention and supplementation of vitamin D deficiency is warranted.

## 1 7. Conclusion

2 Vitamin D deficiency is a common finding worldwide. In older individuals, vitamin D deficiency is a  
3 highly prevalent particularly in certain risk populations such as institutionalized or homebound  
4 individuals. Longitudinal studies of 25(OH)D concentrations demonstrate that the mean  
5 concentrations remains fairly stable over time. However, there is high interindividual variation in  
6 changes in 25(OH)D concentrations which cannot be solely explained by vitamin D supplement use.  
7 Vitamin D deficiency in older individuals contributes to increased fracture and fall risk and a decline  
8 in physical function. In addition, vitamin D deficiency has been related to numerous other age-  
9 related diseases such as cardiovascular disease, diabetes mellitus type 2 and cancer, although a  
10 causal relationship with these outcomes remains uncertain.

11 Several mechanisms that play a role in vitamin D metabolism and activity are age-dependent.  
12 Intestinal calcium absorption decreases over time. VDR number decreases with aging in several  
13 organs involved in calcium metabolism such as intestine, bone and kidney. In the kidney and bone  
14 and probably also other organs, CYP27B1 activity decreases with aging reducing local activation of  
15 25(OH)D. Cellular aging is also influenced by 1,25(OH)<sub>2</sub>D. Effects of 1,25(OH)<sub>2</sub>D on cell proliferation  
16 and differentiation may play a role in potential anti-cancer effects whereas regulation of telomere  
17 length may result in longevity. The role of these effects in humans in vivo, however, remains to be  
18 further explored. The final question is whether therapy targeted at the VDR can reverse age-related  
19 processes such as the development of osteoporosis and muscle atrophy.

20 Moderate dose vitamin D supplementation results in prevention of fractures, falls and functional  
21 decline in older individuals. Currently, several large vitamin D supplementation trials are being  
22 conducted and these will give the final answer regarding usefulness for the so-called “non-classical”  
23 outcomes. Meanwhile, prevention of vitamin D deficiency and supplementation with vitamin D  
24 supplements warrants special attention particularly in older populations. For older individuals

- 1 moderate dosages of 800IU-1000IU daily are advised. High (>50.000 IU) less frequently administered
- 2 dosages of vitamin D should be avoided because of a potential increased fall and fracture risk.

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38

Highlights: 3 to 5 bullet points (maximum 85 characters, including spaces, per bullet point).

- Vitamin D deficiency is very common worldwide
- Aging in humans results in less metabolic activity of vitamin D.
- Aging leads to a decrease in vitamin D receptor number in several organs
- Vitamin D may influence cellular aging through effects on telomere biology.