



REVIEW

THE “SUNSHINE” VITAMIN (D) IN OLDER ADULTS: BEYOND BONE HEALTH

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ABSTRACT

Vitamin D deficiency is reaching alarming levels worldwide and it is highly prevalent in older adults. The association of vitamin D deficiency and osteoporosis has been well studied but in the last decade numerous studies have been exploring the efficacy of treating vitamin D deficiency in order to prevent or treat other common conditions found in the older population. There is robust evidence that vitamin D supplementation together with calcium prevents fracture risk, but there is equivocal evidence with regards to falls reduction. There is no substantial evidence that it decreases frailty, sarcopenia, cognitive impairment, depression and the risk of cardiovascular or diabetes. Research is showing that vitamin D supplementation may prevent acute respiratory tract infections and COPD exacerbations and it might also decrease cancer mortality. Screening for vitamin D deficiency is recommended in all older adults with musculoskeletal diseases and in COPD patients hospitalised with an exacerbation. There is still controversial evidence for the optimal recommended supplementation dose, but most guidelines recommend around 800 IU of vitamin D daily as a maintenance dose for bone health. Despite the established benefits that vitamin D has on musculoskeletal health, it is still unclear if sufficient vitamin D and vitamin D supplementation will benefit the other common conditions. Therefore, future well-designed randomised controlled studies are still needed.

Keywords: Vitamin D; older adults; osteoporosis; frailty; sarcopenia; COPD

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BACKGROUND

Older adults especially those in institutionalised care are at a higher risk of vitamin D deficiency. The skin's concentration of 7-dehydrocholesterol decreases at around 10 to 15% for each decade after 40 years. Moreover, older adults might be more prone to experience limited sun exposure due to shorter times spent in outdoor activities. Poor nutrition has also been associated with vitamin D deficiency and comorbidities such as liver, kidney diseases and polypharmacy may also contribute to increased risk of deficiency (1)

In the last decade numerous studies have been exploring the efficacy of treating vitamin D deficiency in order to prevent or treat common conditions found in the older population. The association of vitamin D deficiency and osteoporosis has been well studied, but other studies suggest that it may play a role in decreasing falls and improve muscular function, cognition, mood, cardiovascular, respiratory disorders, endocrine disorders, immunity and decrease cancer mortality.

Since vitamin D deficiency is reaching alarming levels worldwide (2,3), and the range of potential benefits of vitamin D effects are potentially wide, doctors might encounter dilemmas on the appropriate clinical approach to tackle deficiency in their older patients. The focus of this paper is to review the current research on vitamin D in relation to older adults and to look into the clinical approaches to tackle vitamin D deficiency.

THE SUNSHINE VITAMIN

Vitamin D is also called the sunshine vitamin as it is a fat-soluble vitamin mainly produced by the skin after direct sun exposure. 7-dehydrocholesterol found in skin upon exposure to ultraviolet B is broken down to produce the pre-D isomers. In a non-catalytic process these get rapidly converted to cholecalciferol (vitamin D3). In a much lesser extent it can be obtained from food sources (calciferol-vi-

tamin D2 and vitamin D3) such as egg yolk, oily fish and fortified foods. Often, if replacement is needed it can be achieved by medical supplementation. Vitamin D is converted to 25-hydroxyvitamin D in the liver, which is the major circulating metabolite of vitamin D that can be measured in serum. 25-hydroxyvitamin D is converted in the kidney to its active form 1,25-dihydroxyvitamin D. This active form is also known as "calcitriol" and it plays a pivotal role in regulating calcium metabolism. The enzyme responsible to convert vitamin D in its active form is 1- α -hydroxylase which is also found peripherally in various tissues (1).

VITAMIN D AND MUSCULOSKELETAL HEALTH

Vitamin D deficiency leads to decreased calcium intestinal absorption, leading to a rise in parathyroid hormone levels and increased bone turnover. This subsequently results in osteopenia and osteoporosis. Several molecular mechanisms have been suggested on how vitamin D effects muscle strength, metabolism, myogenesis, mitochondrial activity, glucose metabolism and muscle regeneration. The exact mechanisms, their regulation and action of vitamin D-related pathways are still unclear (4). A recent Cochrane systematic review analysed 53 trials with a total of 91,791 participants and found that vitamin D supplementation alone is highly unlikely to be effective in preventing fractures (11 trials, 27,693 participants; risk ratio (RR) 1.12, 95% confidence interval (CI) 0.98 to 1.29), but together with calcium supplementation there is high quality evidence that it can decrease the risk of any type of fracture (10 trials, 49,976 participants; RR 0.95, 95% CI 0.90 to 0.99) (5). Similar results were found in a pooled analysis of 68,500 patients from major vitamin D fracture trials in Europe and USA (6). The above reviews continue to emphasise that calcium and vitamin D work synergistically on the bone and thus decrease the risk of fragility fractures.



VITAMIN D AND FALLS

Falls in older adults cause considerable morbidity and mortality and older people experience a decrease in daily functional status after an injurious fall. In a review that included 95 trials from care facilities and hospitals (138,164 participants), it was concluded that there is moderate-quality evidence that vitamin D supplementation might reduce the rate of falls in patients with vitamin D deficiency (4 studies, 4512 participants, RR 0.72, 95% CI 0.55 to 0.95), but does not impact the risk of falling. The authors of this Cochrane review acknowledge that most of the trials included were at high risk of bias in more than one domain (7). A meta-analysis found vitamin D supplementation to have little effect on the risk of falls, whilst the “Study to Understand Fall Reduction and Vitamin D in You” (STURDY) noted that doses of more than 1000 IU/day of vitamin D potentially increased the risk of falls, whilst 200 IU/day did not (8). The conclusions from the STOP-IT trial showed that older adults with vitamin D of <20 ng/ml are likely to benefit from vitamin D supplementation that brings them in the range of 20-40 ng/ml. Older adults with a serum vitamin D between 20-40 ng/ml do not benefit from supplementation, whilst those with a vitamin D level of more than 40 ng/ml are likely to have increased risk of falling if they are on vitamin D supplementation (9).

VITAMIN D AND SARCOPENIA

Vitamin D may diminish the expression of myostatin in muscles, which inhibits muscle growth leading to an increase in muscle cell proliferation. Vitamin D receptors (VDRs) also seem to stimulate protein synthesis in muscles. Moreover, it plays an important role in calcium and inorganic phosphate metabolism which are needed for muscle contraction. These different mechanisms might be the reason why vitamin D has an important role in maintaining the physiological function of skeletal muscle. Probable sarcopenia is when there is low muscle strength, and sarcopenia is confirmed if there is ad-

ditional low muscle quality or quantity. Severe sarcopenia is present when this leads to poor physical performance. Sarcopenia can result in poor mobility, limited performance of activities of daily living, impaired quality of life and increased risk of hospitalisation and institutionalisation. There is also a positive association between sarcopenia and osteoporosis leading to increased risk of vertebral and hip fractures. Vitamin D deficiency has been attributed as one of the possible causes of sarcopenia. A meta-analysis of randomised controlled trials by Gkekakos et al., (10) (8 eligible studies with 776 patients) showed that vitamin D supplementation between 100-1600 IU daily plus protein (10-44 g/day) supplementation resulted into a positive effect on muscle strength, as there was an improvement in handgrip strength (SMD 0.38 ± 0.07, 95% CI 0.18-0.47, p=0.04) and a decrease in sit-to-stand time (SMD 0.25 ± 0.09, 95% CI 0.06–0.43, p = 0.007; I² 0%) when compared to placebo. There was no improvement found in appendicular skeletal muscle mass or muscle performance. Similar results were found in another recent meta-analysis by Cheng et al., (2021), [9 RCTs, n=1420] when combining vitamin D, protein and exercise.

FRAILITY

Frailty is a clinical state in which an individual is more vulnerable to stressors due to a decline in physiological reserve. This increases the risk of dependency, mortality and institutionalisation. Vitamin D deficiency has been observed to be higher in frail older adults and there is conflicting evidence if this is a direct risk. A recent meta-analysis by Ju et al., (2018) of more than 20,000 participants demonstrated that there is a statistically significant inverse association between serum vitamin D levels and the risk of frailty. This relationship was also present after adjusting for other known risk factors. A rise of 25 nmol/L in vitamin D resulted in an 11% decrease in the incidence of frailty in prospective studies and 12% decrease in the risk of frailty in cross-sectional studies.

A daily intake of 1000 IU of vitamin D supplementation was needed to increase vitamin D concentrations by 25 nmol/L. One should appreciate the complexity between this link as frailty itself may lead to vitamin D deficiency since the individual will be less likely to do outdoor activities and could also have poor nutritional intake. Another recent review also indicates that lower vitamin D levels are linked to frailty. Quantitative analyses showed significant differences in the comparisons of frail (standardised mean difference (SMD)—1.31, 95% CI (-2.47, -0.15), $p = 0.0271$) and pre-frail (SMD—0.79, 95% CI (-1.58, -0.003), $p = 0.0491$) participants vs. non-frail participants (13). The findings of the above studies should be interpreted within their limitations due to several factors such as the different definitions of frailty used, the heterogeneity of the included studies and the studies included were not randomised controlled trials.

COGNITIVE IMPAIRMENT

VDRs are located in the brain cortex and hippocampus which are crucial for cognitive function and therefore their loss has been associated with cognitive impairment. Vitamin D has an important role in neurotransmission, neuroprotection and neuroplasticity. A recent meta-analysis of 18,974 participants showed that vitamin D deficiency (<10 ng/ml) increased the risk of cognitive impairment by 54% (14). Chai et al., (2019), when analysing 12 prospective cohort studies and four cross-sectional studies noted significant associations between vitamin D deficiency and dementia which was stronger with levels of vitamin of less than 10 ng/ml (severe deficiency). They admit that the included studies are affected by reverse causality biases and therefore cannot conclude if the vitamin D deficiency is causing the dementia or the dementia is caused by reduced vitamin D intake and less outdoor activities. One trial of 4143 participants found that vitamin D3 (400 IU/day) together with calcium supplementation had no effect at any time-point up to 10 years

on cognitive function or the incidence of cognitive impairment. Another study with 60 participants also showed no beneficial effect of vitamin D3 (4000 IU/day) on cognitive function over a 6 month period (16).

MOOD DISORDERS

Having low vitamin D status has been hypothesised to play a role in mood disorders. As mentioned earlier, VDRs are present in different brain areas. In addition, vitamin D helps in the production of serotonin leading to a general protective and stimulating effect on brain tissue. Some meta-analyses suggest that vitamin D supplementation might help to treat depression (17) and Cheng et al., (2020), showed that vitamin D supplementation was also associated with a reduction in negative emotions. These results are not consistent, as other meta-analyses have contradictory evidence (19). This may be explained by the fact that the described studies included patients with depressive symptoms and adequate vitamin D levels. A recent systematic review by Guzek et al., (2021), failed to provide significant evidence to demonstrate a positive effect of vitamin D on mood as the majority of included studies showed inconclusive results. One study showed that for vitamin D to have a beneficial effect on depressive symptoms it needs to be combined with physical activity and that dietary intake is far better than supplementation. It was concluded that vitamin D should be part of a broader treatment program which should also include physical activity.

CARDIOVASCULAR DISORDERS

A few studies have shown that there might be a link between vitamin D deficiency and increased risk of stroke and cardiovascular disease (CVD). A meta-analysis of 25 studies with 10,099 participants showed that vitamin D deficiency is associated with an increased the risk of CVD by 44% (21). In another systematic review of 299 patients (22), vitamin



D supplementation was positively associated with diastolic blood pressure and parathyroid hormone, but had no significant effects on hs-CRP mean difference, triglyceride levels, total cholesterol and low and high density lipoproteins. The anti-hypertensive function of vitamin D may be through the suppression of the renin-angiotensin-aldosterone pathway, direct effects on the endothelial cells and calcium metabolism, and the secondary prevention of hyperparathyroidism (22). In a recent large meta-analysis of more than 83000 participants vitamin D supplementation was not found to decrease major adverse cardiovascular events, individual CVD endpoints (myocardial infarction, stroke and CVD mortality) (23). Due to lack of consensus on the association between vitamin D levels and CVD, there is no clear message on vitamin D supplementation and reduction of CVD.

RESPIRATORY CONDITIONS

Public and research interest in relation to vitamin D supplementation and prevention of acute respiratory infections has increased since the COVID-19 pandemic. As VDRs are expressed in immune cells, vitamin D plays an essential role in the modulation of the innate and adaptive immune system. Laboratory studies have indicated that vitamin D metabolites support innate immune responses to respiratory viruses and some observational studies have shown an independent association between vitamin D deficiency and increased risk of respiratory infections. A recent meta-analysis by Jolliffe et al., (2021), showed that vitamin D supplementation (mostly between 400-1000 IU), was safe and overall decreased the risk of acute respiratory tract infections when compared to placebo. There was significant heterogeneity across the trials and all ages were included. The relevance to COVID-19 infection is still unknown. Vitamin D deficiency is common in COPD patients and a systematic review and meta-analysis of 560 participants (aged between 40-86 years) showed that vitamin D supplementation decreased the rate of moderate/severe COPD

exacerbations in patients with a low serum vitamin D at baseline (25).

ENDOCRINE CONDITIONS

Type 2 diabetes mellitus (T2DM) is one of the most common and disabling conditions in older adults. It is mostly diagnosed after 60 years of age and it is expected to increase in the next two decades (26). Some observational studies have indicated that vitamin D deficiency is inversely associated with the incidence of T2DM as deficiency leads to less insulin production and secretion. Moreover, in peripheral insulin-target cells vitamin D may decrease insulin resistance. Other studies in older adults, after adjusting for potential confounders such as obesity, have reported no significant association between the two (27). In contrast to the younger generations, older adults may be less prone to the health hazards of vitamin D deficiency. Lucato et al., 2017, followed 28,258 participants with a mean age of 67.7 years for 7.7 years and showed that lower levels of vitamin D were associated with an increased risk of developing diabetes. A meta-analysis of 4896 subjects showed that vitamin D supplementation significantly reduced the risk of T2DM in non-obese subjects. One should note that participants in the included eligible studies were not limited to older adults (mean age of 53.7 years (27). In contrast, another meta-analysis provided no evidence that vitamin D supplementation had beneficial effects on peripheral insulin sensitivity in participants with or at risk of insulin resistance (28). To date, there is little evidence that vitamin D supplementation helps achieve glucose homeostasis, decrease the risk of progression from prediabetes to T2DM, or helps manage the condition (29).

CANCER

VDRs are found throughout the body and the binding of vitamin D with its receptor causes transcriptional activation and repression of target genes. This results in apoptosis, antiproliferative

effects, and immunomodulatory effects that may result in a reduction of fatal cancer and metastatic disease (30). The VITamin D and OmegA-3 Trial (VITAL) was a large (25,871 U.S participants; mean age 67.1; 51% female) randomised, placebo-controlled, 2x2 factorial trial of 2000 IU of vitamin D and marine omega-3 fatty acids. This study showed that vitamin D did not significantly reduce the incidence of invasive cancer but showed a reduction in total cancer mortality. An updated meta-analysis of this large study and other vitamin D controlled trials, also showed a significant reduction in cancer mortality but not in the incidence (31) A secondary analysis of the VITAL randomised control trial showed that 1617 participants were diagnosed with invasive cancer over a median period of 5.3 years. No significant difference in cancer incidence was also found in the treatment arm, but a significant reduction in advanced cancer (metastatic or fatal) was found in those receiving vitamin D supplementation (2000 IU). This was noted in those with normal BMI and not amongst those that were overweight or obese (30). Keum et al., (2019), and Bjelakovic G et al., (2014) further support that vitamin D supplementation significantly decreases total cancer mortality but there is no evidence that it decreases or increases cancer occurrence. One should note that these findings could be due to risks of type I errors (too few participants and attrition bias) (33).

CLINICAL APPROACH

Vitamin D screening

According to the National Osteoporosis Society (34) the best way to measure vitamin D status is to measure plasma 25(OH)D. This is only recommended for older adults with musculoskeletal symptoms due to probable vitamin D deficiency, older adults having bone diseases that may be improved with vitamin D supplements, and patients with bone diseases where correcting vitamin D deficiency may be necessary prior to giving treatment. The US Preventive Service Task Force also does not recommend blind-

ly screening asymptomatic patients (35). Routine monitoring of plasma vitamin D may be needed in patients with symptomatic vitamin D deficiency, malabsorption or when poor compliance to medication is suspected. The GOLD scientific committee in relation to treatment of COPD exacerbations, recommends that all patients hospitalised for COPD exacerbations should be screened and investigated for severe vitamin D deficiency and if found, should be managed accordingly (36).

Vitamin D supplementation and treatment of deficiency.

Many professional societies and countries around the world have different recommendations on the adequate daily vitamin D intake. These differences could be due to an incomplete understanding of the health benefits of this vitamin and the guideline purposes. Although sun exposure is the major source of vitamin D for some people, the National Institutes of Health based their RDAs values on the assumption that people receive minimal sun exposure. Their recommended vitamin D daily intake to maintain bone health and calcium metabolism in older adults ≥ 70 years of age is of 800 IU (29), which is the same as the Endocrine Society (1). The National Osteoporosis Society and the National Academy of Medicine recommend that adults more than 50 years old should consume between 800 to 1000 IU of vitamin D daily (34). In contrast, Public Health England recommends that adults at risk of vitamin D deficiency (example the frail older adults with limited sun exposure and those in institutionalised care), should take 400 IU of vitamin D daily all year round (37).

There are also diverse opinions with regard to the level threshold of vitamin D deficiency. The Scientific Advisory Committee on Nutrition and the Institute of Medicine propose that the following are adopted by practitioners in respect to bone health: vitamin deficiency as a value of <25 nmol/L (<10 ng/ml), inadequate between 25-50 nmol/L (10-25 ng/ml) and sufficient as >50 nmol/L (>20 ng/ml). In



vitamin deficiency, oral vitamin D3 should be prescribed and rapid correction of deficiency is usually needed in patients with symptomatic disease or about to start treatment with antiresorptive agents (potent medications like zoledronate, denosumab or teriparatide). A loading regimen of 300,000 IU vitamin D is given either in weekly or daily doses over six to 10 weeks and afterwards, a maintenance daily dose of 800-2000 IU daily is given (see Table 1). Unless a very urgent correction of vitamin D deficiency is needed, high bolus loading of vitamin D should be mostly avoided as there could be an increased risk of falls and fractures. When the correction of vitamin D deficiency is less urgent or when starting oral antiresorptive treatment, a loading dose may be unnecessary. After a month, it is recommended to check an adjusted plasma calcium in case there is unmasking of primary hyperparathyroidism (34).

Vitamin D treatment in special groups

Older adults with chronic kidney disease (CKD) should have their vitamin D replaced as per other older adults. In patients with CKD stages 3-5 with progressively increasing intact parathyroid hormone, should have individualized treatment with active vitamin D such as vitamin D analogue (example alfacalcidol). Ideally, in end stage renal failure

advice should be sought from a renal physician regarding monitoring and replacement requirements (38).

A suggested regimen for vitamin D deficiency due to intestinal malabsorption or chronic liver disease is to use Ergocalciferol 300,000 IU by intramuscular injection. Vitamin D levels should be monitored again after 3 months (39).

Vitamin D toxicity

Vitamin D toxicity is a rare occurrence and usually occurs either through accidental overdosing or inappropriate high-dose treatment. It usually manifests with signs and symptoms of hypercalcaemia (confusion, polyuria, polydipsia, anorexia, vomiting or muscle weakness). Most of the cases recover without complications, but rarely profound hypercalcaemia can lead to acute renal failure. Less severe symptoms of excessive vitamin D is prolonged hypercalciuria, which can increase the risk of renal stones. Intake of vitamin D of less than 10,000 IU daily is not associated with toxicity, whilst doses equal to or above 50,000 IU daily for weeks or months can lead to toxicity. To avoid this, the IOM set the upper limit for maintenance dose of 4000 IU daily. The management of vitamin D toxicity is mostly supportive and targets to lower serum calcium levels and avoid acute kidney injury. All vitamin D and calcium supplementation should be stopped and one should avoid bed rest to prevent hypercalcaemia of immobilization. Hypercalcaemia and acute kidney injury should be treated accordingly (34).

Table 1. Examples of Loading and Maintenance Regimes for the treatment of vitamin D deficiency (the list is not exhaustive). (34)

Guidance for treatment of vitamin D deficiency	
Example Loading Regimes *(tablets, capsules or liquid)	
	50,000 IU once weekly for 6 weeks (300,000 IU)
	40,000 IU given weekly for 7 weeks (280,000 IU)
	1,000 IU tablets, four a day for 10 weeks (280,000 IU)
	800 IU capsules, five a day for 10 weeks (280, 000 IU)
Example Maintenance Regimes *(tablets, capsules or liquid)	
	20,000 IU every 4 weeks
	25,000 IU every 4 weeks
	800 to 2000 IU daily

CONCLUSION

Despite the established benefits that vitamin D has on musculoskeletal health, it is still unclear if sufficient vitamin D and vitamin D supplementation will benefit the other common conditions in the older population (see Table 2). Future well-designed randomised controlled studies are still needed.

Table 2. Summary on the effectiveness of vitamin D in relation to the most common geriatric disorders.

Summary on the effectiveness of vitamin D		References
Fractures	Vitamin D supplementation alone is unlikely to be effective but when given with calcium it significantly decreases fracture risk.	Abrahamsen et al., 2010; Avenell Alison et al., 2014
Falls	Equivocal evidence on vitamin D supplementation and risk of falling.	Appel et al., 2021; Cameron et al., 2018
Sarcopenia	No substantial evidence (few numbers of RCTs in meta-analyses) that vitamin D supplementation improves muscle power.	S. H. Cheng et al., 2021; Gkekas et al., 2021
Frailty	Vitamin D supplementation might decrease frailty but most studies conducted were not RCTs and had high heterogeneity.	Ju et al., 2018; Marcos-Pérez et al., 2020
Cognitive Impairment	Equivocal evidence on vitamin D supplementation and cognitive impairment.	Chai et al., 2019; Rutjes AWS et al., 2018
Mood Disorders	Equivocal evidence on vitamin D supplementation and mood disorders. Supplementation if given should be part of a broader treatment program.	Y. C. Cheng et al., 2020; Guzek et al., 2021
Cardiovascular Disorders	Until now no clear evidence on vitamin D supplementation and reduction of CVD.	Bahrami et al., 2020; Barbarawi et al., 2019; Gholami et al., 2019
Respiratory Conditions	Vitamin D supplementation might decrease the risk of acute respiratory tract infections and the rate of moderate/severe COPD exacerbations.	Jolliffe et al., 2019, 2021
Diabetes	No substantial evidence that vitamin D supplementation reduces the risk of diabetes or helps manages the disease.	Pramono et al., 2020; Zhang et al., 2020
Cancer	Vitamin D does not decrease cancer incidence but RCTs showing that it may decrease cancer related mortality.	Bjelakovic G et al., 2014; Keum et al., 2019; Manson et al., 2019

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