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Research Paper

Why and how to administer Vitamin D supplementation in the elderly?

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ABSTRACT

Vitamin D deficiency as a special form of undernutrition has been discovered since ca. 100 years ago. Vitamin D deficiency in the elderly, is a frequent type of lack of micronutrient. Mainly, low levels of dietary intake and short period of exposure to sunshine are mentioned as its main origins. In the elderly, diminished endogenous formation of active form of vitamin D also plays a role. The hypovitaminosis D (HVD) results in several dysfunctions like bone homeostasis abnormalities, muscular weakness, cardio-metabolic diseases, neurological or immunological frailty, etc. The supplementation is advisable in the elderly because of the physiological shrinking of organ functions (skin, liver, kidney, muscle, etc.). The recommended dose for the elderly depends on the serum levels, usual dose varies between 400 and 3000 IU/day, but overdose with oral administration is very rare.

Key words: Vitamin D, elderly, hypovitaminosis, supplementation, dosage.

INTRODUCTION

Active form of Vitamin D (VD) is an essential fat-soluble compound produced by the body from precursors after exposing the skin to UV-B irradiation and transformation in the liver and kidney. Despite the endogenous production, high prevalence of hypovitaminosis is detected in several areas of the world (Rothenbacher et al., 2014; Yu et al., 2014 ; Williams et al., 2014; Alzaheb, 2018; Kamboj et al., 2018; Annweiler et al., 2017) . The impact of VD is known in the musculoskeletal as well as in extraskeletal organs. Due to many reasons which will be discussed later on, elderly people are at higher risk of HVD than younger ones, therefore their control and supplementation with vitamin D, if needed, is very reasonable.

Vitamin D – under physiological conditions – is produced in the skin from 7-dehydrocholesterol and/or is taken up from dietary sources in form of vitamin D_2 (plant origin) and vitamin D_3 (animal origin). The endogenous production is often inadequate especially nowadays, due to lack of exposure to sunshine, for example, wearing closed cloths, living in institution and because of the high air pollution (Caccamo et al., 2018) . The serum levels of <10 ng/ml (25 nmol/L), the <20 ng/ml (<50 nmol/L) and 20-30 ng/ml (50-75 nmol/L) are usually considered as severe vitamin D deficiency, VD deficiency and VD insufficiency, respectively. If vitamin D supply results in less than 75 nmol/L blood concentrations, this dispose human beings to comorbidities.

A recent study revealed that by increase in age, VD deficiency is steadily increasing (Williams et al.,2014). Elderly people living in institutions are more jeopardized to hypovitaminosis.

THE BIOCHEMICAL BACKGROUND

The symptoms of rachitis have been described by Socrates BC. Vitamin D deficiency as a special form of undernutrition has been unravelled ca. 100 years ago. First identification of vitamin D goes back to the twenties of last century in the bulk of UV-radiated ergosterol. This was a crude mixture called vitamin D_1 but later it became clear that this was a mixture of various sterine-type compounds. Further purification led to the crystallized ergocalciferol (vitamin D_2). Some years later, research with UV-irradiation of the 7-dehydrocholesterol resulted in cholecalciferol (vitamin D_3) as indicated in Figure 1. It was later verified that vitamin D_2 is actually a plant origin compound (derived from ergocalciferol) and the vitamin D_3 is of animal origin

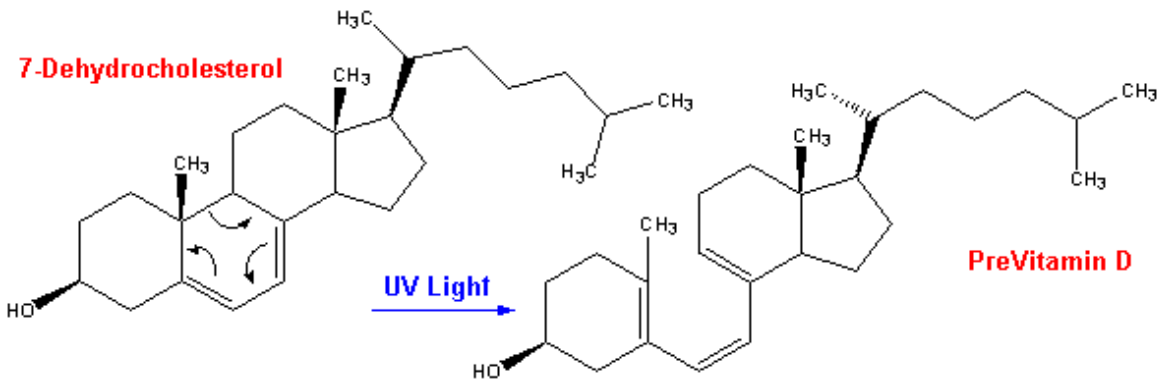

Figure 1: The formation of Vitamin D in the skin: the first step.

(derived from 7-dehydrocholesterol). Both of them undergo 25-hydroxylation first in the liver and later on one more hydroxylation step in the kidney on position 1 finally resulting 1,25-$(OH)_2$-vitamin D. Therefore 25-hydroxy-cholecalciferol often named as calcidiol and 1,25-dihydroxy-cholecalciferol (1,25-dihydroxy-vitamin D or 1,25-$(OH)_2$-VD) named as calcitriol (abbreviated 1,25-DHCC). The physiological vitamin D effect is attributed to the final (active) metabolite calcitriol, however the name vitamin D is used to one or mixture of metabolites VD_2 and VD_3 (correctly would be "vitamins D"). Vitamin D dose is usually given in International Units (IU), 1 IU = 25 ng cholecalciferol-equivalent compounds.

THE PHYSIOLOGY OF VITAMIN D

Although VD is not synthesized and released from an endocrine gland, it has hormone-like pathway and functions similar to many other steroids. VD has an indispensable role in the calcium/phosphate homeostasis and bone-metabolism. The regulatory role in calcium homeostasis is shared with parathyroid hormone (PTH), the calcitonin and the activated VD, the calcitriol (1,25-dihydroxyvitamin D). The discovery of vitamin D receptors presence in various organs opened the research of extraskeletal VD effects. A lot of conditions affect the vitamin D levels of the population. In the elderly (>70 years), the VD producing capacity is ca. 75% lower than that in people of 20 years old. Kidney disease impairs biotransformation of calcitriol but various extrarenal cells may produce 1,25-(OH)2-cholecalciferol as well. The fear of melanoma put many individuals to avoid sunshine and thus development of HVD. Old and frail patients living in nursing homes are also in elevated risk of hypovitaminosis D (Arnljots et al., 2017).

Calcitriol plays a crucial role in the gut-absorption of Ca^{++}; in absence of 1,25-$(OH)_2$-VD, the mineralization of osteoid tissue is decreased which results in rachitis (childhood) and osteomalacia (elderly). Calcitriol also controls (together with PTH) expression of RANKL (receptor activator of nuclearfactor κB), which is important in osteoclast differentiation further some paracrine regulators. In the bones, 1,25-DHCC stimulates resorption of calcium. In the parathyroid gland, VD-receptors block parathyroid hormone gene expression thus controlling proliferation of parathyroid cells. In the kidney, calcitriol weakly stimulates Ca^{++}-reabsorption into the blood. In the "non-classical" field of VD effects the regulation of renin-angiotensin system and the insulin resistance has been recently unravelled.

Hypovitaminosis D in the elderly

Normal VD levels are between 75-175 nmol/L (30-70 ng/ml) however, data in publications vary in this respect. The definition and grading of deficiency may depend on the cut-off point that vary according to countries, researchers and intentions (manufacturers). In the USA, 60% of nursing home residents and 57% of hospitalized patients were found to be vitamin D deficient (Tangpricha and Khazai, 2019). In Poland, VD deficiency of varying severity has been published in 90% (Rusinska et al., 2018). In the very old population, (>80 years old) prevalence of hypovitaminosis D is higher than that in the younger ones. Most serious result of HVD is hypocalcemia with consequential adverse effects, examples, muscle cramps, convulsions and under very serious conditions, tetany, furthermore, in long-term VD-insufficiency osteomalacia may develop. Several publications demonstrate that even subclinical HVD is the cause of several chronic disease and/or worsens morbidity prevalence in the aged (>50 years old) (He and Hao, 2019; D'Amelio and Quacquarelli, 2020).
Vitamin D deficiency may develop as follows:

a. Vitamin D deficiency is highly prevalent in malnourished patients and negatively associates with long-term mortality in the old age.

b. Decreased dietary intake. Main reason is intestinal malabsorption as celiac disease, short bowel syndrome,

gastric bypass, inflammatory bowel disease, and steatorrhoea caused by biliary blockage or pancreatic disease.

c. Decrease in exposure to sunshine: people living in the north or south (latitude greater than 40˚ in both directions) or when the skin is covered with cloths, for example, Muslim women. (Ca. 20 minutes skin exposure to UVB radiation in more than 40% of the body surface is enough to cover the daily requirement). Extensive use of sun screens also results in increased risk of hypovitamin D as well as the high grade of industrial air pollution. The institutionalized and/or hospitalized elderly people are also often in lack of adequate exposure to sunlight.

d. Organ dysfunction: healthy kidney function is needed for the 1α-hydroxylation reaction, otherwise secondary hyperparathyroidism and renal bone disease may develop. Healthy liver is needed to the 25-hydroxylation of precursors vitamin D2 and D3. This is the usual problem in liver cirrhosis.

e. High levels of calcitonin inhibit 1,25-DHCC production by the kidney.

f. Low levels of vitamin D-binding protein due to genetic polymorphism may diminish transport to the target organs liver and/or kidney

g. Increased deactivation of the active vitamin D due to drug interaction (induction of metabolizing enzymes)

The melanin production, which compound is very effective UVB absorber, often decreased in the elderly skin pigmentation, thus the dermic synthesis of VD is also reduced in this group of patients.

Further, it is to note that fasting itself may block the bioactivation of previtamin D via repression of hepatic enzyme CYP2R1, that is, the predominant 25-hydroxylase in the liver and via upregulating CYP24A1, that is, it is responsible for the deactivation of 1,25-$(OH)_2$-cholecalciferol in the kidney. Similar CYP2R1 effect and subsequent decrease in vitamin D serum levels is caused by diabetes mellitus Type 1 and 2, according to the animal studies(Aatsinki et al.,2019).

THE CONSEQUENCES OF LOW VITAMIN D LEVELS

Vitamin D deficiency leads to decrease in Ca^{++}-absorption and that results in hyperparathyroidism with subsequent phosphaturia and accelerated bone demineralization. Administration of calcium and VD is particularly important for the prevention/treatment of age-related loss of bone density and skeletal muscle mass because the VD alone did not result in improvement (Avenell et al., 2009). As minerals in general should be in physiological balance, especially the ions with identical valence, magnesium also plays a crucial role in the bone homeostasis and in muscle function. Magnesium deficiency affects VD levels as well: it is needed to enzymatically activate vitamin D in the liver and kidney (Erem et al., 2019).

The decrease in muscle strength depends also on the vitamin D disposal. Halfon et al.(2015) reported a direct effect of VD on the muscle cells via transmembrane receptor (Halfon et al., 2015). Thus, the low VD levels are – at least partly – responsible for falls and frailty.

There is a strong evidence that insufficient levels of VD may lead to cognitive dysfunction. Lukaszyk et al.(2018) recently published a study with 357 elderly patients in which it has been demonstrated that higher vitamin D serum levels are associated with better cognitive performance (Lukaszyk et al.,2018). In contrast, low levels of VD were detected in depression patients but no improvement in depression after administration of vitamin D has been reported.

In obstructive lung disease, asthma-COPD overlap syndrome (ACOS) correlate with 25-OH-vitamin D deficiency, however, asthma and COPD alone does not strongly correlate with VD deficit (Odler et al.,2015).

In elderly patients with various cardiovascular diseases, HVD is frequent and the supplementation of VD may decrease CV risk, in general. Presence of cardiometabolic syndrome, especially some of the constituents like waist circumference, high cholesterol and HDL levels positively associate with the presence of hypovitaminosis D (Al-Dabhani et al., 2017). In the institutionalized patient population, VD administration usually decrease overall mortality in the elderly (Meehan and Penckofer, 2014). Earlier, there was a hypothesis that vitamin D supplementation may improve hypertension. But neither recent meta-analyses could confirm the positive association of low serum vitamin D levels and risk of hypertension (Qi et al.,2017) nor RCTs of vitamin D supplementation could support the hypothesis (McMullan et al., 2017). In contrast, deterioration of cardiac function due to remodelling of heart muscle in heart failure patients can be inhibited by vitamin D administration (Zhao et al., 2018). Moreover, it has also been confirmed that low vitamin D levels are not associated with orthostatic hypotension (Laird et al., 2019).

Several publications deal with the association of vitamin D serum levels and cancers. For the time being, only little consistent evidence appeared about this correlation. Inverse correlation is seen for colorectal cancer and VD levels. The low vitamin D levels, however, seems to be risk-increaser of prostate cancer. All other correlations with cancers of various organs are still questionable and there is no reliable recommendation for or against it (Mondul et al., 2017).

In the elderly, gradual development of immunosenescence is present, that is, a quantitative and qualitative defect in the monocytes and macrophages' function is to be detected. This is, at least partly, origin of

Table 1: The potential drug interaction with vitamin D.

Drug	Mechanism of interaction	Result of interaction
atorvastatin	VD increases expression of CYP3A4	reduced atorvastatin levels
bendroflumethiazide	calcium retention by reducing urinary excretion	hypercalcemia w. secondary alkalosis
calcitriol	additive calcium load	hypercalcemia w. secondary alkalosis
carbamazepine	CYP3A4 and 1A2 enzyme inductor	decreased D levels
cardiac glycosides (digoxin)	high dose of VD increase Ca++ levels	secondary arrhythmia caused by hypercalcemia
chlorothiazide	calcium retention by reducing urinary excretion	hypercalcemia w. secondary alkalosis
diltiazem	high dose of VD increase Ca++ levels	decreased effectiveness due to hypercalcemia
hydrochlorothiazide	calcium retention by reducing urinary excretion	hypercalcemia w. secondary alkalosis
orlistat	decreased intestinal absorption of VD	low VD levels w. secondary osteomalacia
paricalcitriol	calcium retention by reducing urinary excretion	hypercalcemia w. secondary alkalosis
phenobarbital	CYP3A4 and 1A2 enzyme inductor	CYP3A4 and 1A2 enzyme inductor
phenytoin	CYP3A4 and 1A2 inductor, inhibitor of Ca++ absorption	CYP3A4 and 1A2 enzyme inductor, hypocalcemia
primidone	CYP3A4 and 1A2 enzyme inductor	CYP3A4 and 1A2 enzyme inductor
statins	VD increases expression of CYP3A4	reduced statine levels, depending on metabol.
steroids (predisone -solone)	reduce calcium absorption	reduces VD action
thiazides	calcium retention by reducing urinary excretion	hypercalcemia w. secondary alkalosis
verapamil	high dose of VD increase Ca++ levels	decreased effectiveness due to hypercalcemia

Legend: Ca = calcium CYP = cytochrom P enzymes VD = vitamin D w = with.

several disease such as infections, cancers, autoimmune diseases. The direct and indirect regulatory role of VD of T cells has been cleared (Cantorna et al.,2015). This may indicate the sporadic beneficial effect of VD supplementation in inflammatory bowel disease and multiple sclerosis and, maybe beneficial as adjunctive therapy for post-transplantation osteoporosis. Through the immunological support VD exert indirectly positive effect on prevention against viral infections, supposedly in the Covid-19 as well. For the latter, there are no strong clinical studies yet.

DRUGS DECREASING OR INCREASING VITAMIN D LEVELS

In the elderly, polypharmacy is a common problem, a lot of elderly patients take more than 5 pharmaceuticals per day. Drugs may interact with vitamin D in the pharmacokinetic as well as pharmacodynamic phase. Most often hepatic metabolism of vitamin D is involved in these effects: cytochrome P450 system is induced or inhibited by several drugs. In the course of biotransformation of pre-vitamin D and pro-vitamin D to 23-OH-cholecalciferol and further to 1,25-$(OH)_2$-cholecalciferol is regulated and catalysed by CYP27B1. In the liver, several other enzymes, like CYP2R1, CYP27A1, CYP2D25, CYP2C11, CYP3A4 have been reported to be capable of VD 25-hydroxylation in vitro. The metabolism of 25-OH-cholecalciferol to 24,25-$(OH)_2$-cholecalciferol is catalysed by CYP24. By this action, the inactivation (degradation) of active form of vitamin D is accelerated. Similar catabolic biotransformation takes place in the liver by CYP3A4 to 4,25-$(OH)_2$-VD and this hydroxylated product at plasma concentration is comparable with 1,25-$(OH)_2$-VD. This metabolic pathway can be inhibited by CYP3A4-specific inhibitors (for example, ketoconazole) and inducible by inductors like rifampin (Wang et al., 2012). Parathyroid hormone is considered to be an important stimulator of CYP27B1 transcription and activity in the kidney (Wang et al., 2012). In contrast, the endogenous fibroblast growth factor-23 (FGF-23), that is increased in kidney disease, and calcium supplementation suppress 1α-hydroxylase (= CYP27B1) responsible for the activation of 25-OH-cholecalciferol by hydroxylation in position C1 (= calcidiol to calcitriol formation).

From clinical perspective, long-term treatment with known enzyme inductors (for example, rifampin) or inhibitors (examples, anticonvulsants, even as adjuvant in pain-relief) may decrease the activation process of VD in the liver and/or the kidney, they can therefore cause low active vitamin D levels. The list of major interactant drugs and their mechanisms are listed in Table 1.

THERAPEUTIC INTERVENTIONS

The best vitamin D supply is the natural sunshine, in the

Table 2: Vitamin D (VD) content of various food in IU/100g.

Food	VD content
fresh eel	1200
fresh wild salmon	600-1200
hering in oil	800
hering, marinated	500-800
salmon, baked/cooked	500-800
salmon, fresh, farmed	100-250
tuna, sardine, canned	200-350
mackerel, baked/cooked	150-800
codfish, fresh	50
liver (pig, ox)	45
milk (whole)	1.5
milk (skimmed)	0
yoghurt (whole milk)	1.5
cheese (hard)	1.5
cheese (feta)	4
egg	40
butter	100
margarine	1000
mushrooms maitake, portabella (raw)	400-1100
mushroom portabella (grilled)	15
mushroom Chanterelle, morel (raw)	200-300
mushrooma shiitake, oyster, white (raw)	10-30
artichokes, asparagus, banboo shoots (raw)	0
beans, broccoli, cabbage, carrots (raw)	0
pear, apple, orange	0

absence of sun, 20-30 minutes of UVB lamp irradiation per day may be used for substitution. If dermal synthesis of VD is not enough, exogenous supplementation is needed. Preferably, nutritional intake of vitamin D precursors helps to keep or reach healthy VD serum levels. The high vitamin D containing foods are to begin with fresh fishes from deep sea. VD content of other foodstuffs are listed in Table 2.

Certain countries especially in the northern latitude, have initiated fortification of various food, in general milk, with vitamin D. This intervention is safe and serve as a cost-effective public health prevention of hypovitaminosis D (Itkonen et al.,2018) .

Besides, there are several forms of vitamin D released for commerce. The dietary supplements contain either ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3). Bioavailability of cholecalciferol is a bit better than ergocalciferol, however, from therapeutic point of view both compounds are equally useful. The successful dose of vitamin D supplementation depends on the grade of hypovitaminosis. As hypervitaminosis/toxicity (serum VD >100-150 ng/ml) is very rare phenomenon if administered orally, usual oral dose of vitamin D is between 400 and 3,000 IU/day (>75 years: 2,000-4,000 IU/d) or 10,000-50,000 NE weekly/biweekly or 50,000-100,000 IU monthly (wide range of doses are reported in various studies!). The three versions of administration are, from therapeutic perspective, equivalent, according to the clinical studies (Rostami et al.,2018; De Niet et al.,2018). Due to the higher loading-dose in VD deficiency, the restoration of normal se-value is shorter in case of monthly one big dose. The lipid-storage of vitamin D is rather good, sudden deficit may not develop.

According to a recent European study of 217 consecutively geriatric hospitalized patients, despite vitamin D supplementation, 44% of them remained VD deficient (Boettger et al., 2018). The reason for therapy resistance can be multitudinous: real resistance is rare however, the low absorption rate, the gaps in adherence and drug interaction resulting in fast inactivation is more frequent.

It is important to stress that vitamin D supplementation should be accompanied by proper daily calcium intake, this means ca. 1 glass of milk (240 mg Ca++) or equivalent amounts of dairy products as shown in Table 3. In calcium supplementation, organic salts of calcium (Ca-citrate, Ca-lactate etc.) are advisable due to better bioavailability.

Additionally, Gorter et al.(2016) published some years ago that main protective factors against severe vitamin D deficiency are VD supplementation, higher daily sun exposure and the regular (and moderate) alcohol consumption (Gorter et al.,2016).

Some years ago, there was a debate about the benefit of high-dose vitamin D administration in the intensive care. The VIOLET study recently confirmed that oral

Table 3: Calcium (Ca++) content of food in mg/100g.

Food	Ca++ content
milk (whole)	125
yoghurt (whole milk)	200
cheese (brie)	540
cheese (cheddar, edam)	700
soya milk	18
egg	60
sardines (canned)	700
salmon (canned)	80
prawns	150
shrimps	125
spinach	150
lentils, kidney beans,	40-70
broccoli	40
Orange	100

administration of 1x 540,000 IU does not provide an advantage over placebo in a period of 90 days on mortality (The National Heart, Lung and Blood Institute, PATEL Clinical Trials Network,2019). Hypervitaminosis D results in hypercalcemia and hypercalciuria but this type of toxicity has been detected very rarely.

CONCLUSION

Vitamin D is an essential micronutrient that is produced by the body if the skin is exposed to sunshine and taken up from daily food. In the elderly, this internal process is diminished and also absorption of vitamin D precursors is decreased therefore to conserve physiological functions additional intake is required. Fortification of food and/or administration of dietary supplements is recommended. The daily dose is depending on the vitamin D status of the elderly individual but some drugs may influence the bioavailability of vitamin D thus consultation with health care professionals is advisable.

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