Vitamin D – Too Little, or Too Much in the Elderly and the Obese?

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ABSTRACT
Vitamin D deficiency became a very popular theme in the medical literature. Thank the global scientific research activity, much is known about vitamin D (VD) however, the sphere of indication of supplementation and the dosage is still a matter in dispute, especially in some groups of patients. A lot of assessment support that more than half of the population is in VD deficit and supplementation is needed. Due to uncontrolled information (internet) and the free availability of VD-containing products, the recommended daily dose is often much less or even more than needed. The risk for hypervitaminosis is existing burden however the symptoms are rarely recognized by the population. This mini-review discuss the main facts and focus to the evidence-based optimal dosage of vitamin D in elevated age and in individuals living with overweight/obesity.

KEYWORDS: Vitamin D; Deficiency; Elderly; Obesity; Dosage; Symptoms

INTRODUCTION
Vitamin D is an essential fat-soluble vitamin. Textbooks give dietary reference intakes according to age, sex, gravidity, lactation, etc. but people are not able to judge their daily VD intake or don’t take the figure or the intentions for need of sunlight exposure seriously. Maybe therefore, high prevalence of hypovitaminosis is detected in almost every area of the world [1-5]. Moreover, women, the elderly and obese people are at higher risk for hypovitaminosis than others.

Vitamin D – under physiological conditions – is produced in the skin, however the endogenous production often is not enough, especially nowadays, due to the high air pollution [6]. Thus, most of VD and its precursors are taken up with food. The endogenously produced and/or from exogenous sources absorbed amounts of VD distributes via circulation into the organs and tissues. The serum levels of <20 ng/ml (<50 nmol/L) and 20-30 ng/ml (50-75 nmol/L) considered as VD deficiency and VD insufficiency, respectively. The low concentrations dispose human beings to comorbidities like cardiovascular, infectious, metabolic, and cognitive disorders.

The supplementation is usually offered by fortified food and dietary supplements or via medical therapy (medicines).

A recent study revealed that by increasing age VD deficiency is steadily increasing [2]. Elderly and obese people are more endangered to hypovitaminosis. Therefore, NIH (USA) recommend an elevated daily dietary allowance (800 IU/D) for individuals above 70 years and for those BMI is >30 kg/m² or obese individuals who have undergone gastric bypass surgery [7]. Here we review the risky conditions and therapeutic options.

Brief Chemical-Biochemical Background
Vitamin D deficiency as a special form of undernutrition has been discovered ca. 100 years ago. Identification of the first vitamin D goes back to the twenties of last century in the bulk of UV-irradiated ergosterol this was a crude mixture called vitamin D1 but later it became clear that this was a mixture of various sterine-type compounds. Further purification led to the crystallized ergocalciferol (vitamin D2). Some years later research with UV-irradiation of the 7-dehydrocholesterol resulted in discovery of cholecalciferol...
(vitamin D3). The step-by-step process is demonstrated in Figure 1. The difference of the vitamins D2 and D3 is just the double bond between C22 and C23 and a methyl radical on C24 (Figure 2), and both provitamins are used as dietary supplement. Their names (-calciferol) refer to their role in Ca++-transport. The basic compound ergosterol contains one hydroxyl-group in the position 3 of the sterane-skeleton. During the gradual metabolism (Figure 3) first in the liver, one more hydroxyl-group addition to the structure in position 25 (25-OH-cholecalciferol), and later on one more in the kidney in the position 1 resulting 1,25-OH2-cholecalcicerol. Therefore 25-hydroxy-cholecalciferol often named as calcidiol and 1,25-dihoxy-cholecalciferol named as calcitriol (abbreviated 1,25-DHCC). The physiological vitamin D effect is attributed to the final (active) metabolite calcitriol however the vitamin D name is used to one our mixture of metabolites VD2 and VD3 (correctly “vitamins D”). Vitamin D dose is usually given in International Units (IU), 1 IU = 25 ng cholecalciferol-equivalent compounds.

In case of VD supplementation magnesium-supplementation can be dangerous because of risk of hypermagnesemia viz. vitamin D increase the intestinal absorption of magnesium as well.

**Brief Physiological Background**

Endogenous production of vitamin D3 originates from acetyl-CoA and is manufactured via multiple steps before reach skin where after UV-B exposure cholecalciferol is born [8]. Although VD is not synthesized by and released from an endocrine gland the vitamin D, as steroid-originated compound, has hormone-like mechanism of action, pathway and functions similar to many other steroids. First, its classical role in the calcium homeostasis and bone-development should be mentioned. The calcium homeostasis is basically regulated by three “calciotropic” hormones: the parathyroid hormone (PTH), the calcitonin and the calcitriol (1,25-dihydroxyvitamin D3). Calcitriol has a decisive role in the intestinal
In the very old population, (>80 y.o.) prevalence of hypovitaminosis D (HypoVD) is much higher than that in the younger counterparts moreover, according to a recent European study of 217 consecutively geriatric hospitalized patients, despite vitamin D supplementation, 44% of them remained VD deficient [10]. In hospitalized very old patients, a higher comorbidity burden is associated with HypoVD, moreover this is a predictor of higher length of hospital stay [11,12]. Most cases of hypovitaminosis D is asymptomatic therefore only a portion of patients with HypoVD gets medical support. Measurement of the muscular functions in the lower extremities may indicate insufficient vitamin D levels. Low VD blood levels are usually accompanied with low calcium and phosphate concentrations, while alkaline phosphatase and PTH levels are elevated. Serious sequel of vitamin D deficiency is hypocalcemia with subsequent convulsions and in the last resort tetany, again, in long-term VD-insufficiency osteomalacia develops. Low vitamin D levels may occur as result of five frequently realized reasons demonstrated in Table 1.

Table 1: The five main conditions initializing hypovitaminosis D in the elderly.

<table>
<thead>
<tr>
<th>Reasons</th>
<th>Explanation</th>
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<tbody>
<tr>
<td>Malabsorption</td>
<td>Gastrectomy, intestinal bypass or resection, inflammatory bowel disease, Crohn’s disease, celiac disease, steatorrhoea caused by biliary blockage, pancreatic disease.</td>
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<tr>
<td>Lack of sunshine</td>
<td>Living in latitude greater than 40°, north or south, skin covered by cloths (eg. Muslim women), sunscreens (fear of melanoma), high grade of industrial pollution, household and institutionalized living conditions.</td>
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<tr>
<td>Chronic kidney dis.</td>
<td>Healthy kidney function is needed for the 1a-hydroxylation reaction, otherwise hyperparathyroidism and renal bone disease may develop.</td>
</tr>
<tr>
<td>Parathyroid Hormone (PTH) Deficiency</td>
<td>Calcitriol production is diminished.</td>
</tr>
<tr>
<td>Calcitonin Over prod.</td>
<td>1,25-(OH)2VD production in the kidney inhibited.</td>
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It should be mentioned that, as known, kidney function – due to decreased renal blood flow – declines by ageing, ca. 10% per decades after 40 years of age. Due to this fact the final activation of precursors of 1,25-(OH)2-D declines by ageing. In severe chronic kidney disease administration of the active 1,25-DHCC is recommended.

However, line of studies demonstrate that HypoVD is causative of several non-skeletal chronic disease as well and worsens morbidity prevalence in the aged (>50 y.o). A pleiotropic effect appears in the extra-skeletal systems: the cardiovascular system, the nervous system, the immune system and the cancerous tissues are affected alike (Table 2). Though in vitro and in vivo (mainly animal) studies demonstrate the disease-inducing effect of HypoVD, human RCTs usually fail to prove preventive or therapeutic beneficial consequence of vitamin D supplementation.

Table 2: The main clinical consequences of hypovitaminosis D and/or vitamin D supplementation in the elderly.

<table>
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<tr>
<th>Consequence</th>
<th>Explanation</th>
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<tr>
<td>Deterioration in bone health</td>
<td>Diminished Ca++ (and Mg++, PO 4-) absorption from gut and subsequent diminished bone mineralization, in the elderly osteomalacia. Dietary support with VD is recommended in the elderly, in combination with calcium.</td>
</tr>
<tr>
<td>Deterioration of skeletal muscle system</td>
<td>Falls in VD deficient elderly women correlates with the HypoVD and supplementation with 700-1000 IU/d significantly improved risk of falls.</td>
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1. Skeletal consequences

2. Extra skeletal consequences

Cancer prevention? controversial results in initiation however positive results in prevention (breast, colon).

Cardiovascular prevention? cardiomyopathy and congestive heart failure in children due to HypoVD are reversible with VD supplementation; strokes, atherosclerosis, coronary artery disease show relationship with HypoVD; inverse association between HypoVD and high blood pressure however RCTs could not confirm the observations.

T2DM A large-scale meta-analysis highlighted the inverse correlation between developing T2DM and VD status. However, no evidence exists that VD supplementation could reduce Type-II diabetes mellitus.

Psychiatric disorders Cognitive impairment of elderly patients is associated with substantial cognitive decline. High dose VD treatment significantly improve depressive symptoms after 1 year

Skin diseases Psoriasis is one of the few non skeletal diseases where the correlation with HypoVD has been demonstrated and the actions of VD have well-validated clinical application.

Liver disease Low vitamin D levels were inversely associated with the histological severity of non-alcoholic liver disease and non-alcoholic steatohepatitis.

Immunity in adaptive immunity, association studies found inverse correlation between VD and/or VD intake and a number of autoimmune diseases.
Beyond the conditions inserted in Table 1, two other factors in connection with pharmacotherapy should be negotiated: the polypharmacy and the medication adherence. There are pharmacological effects that either as side effect or as interaction may decrease VD levels of individuals. Long-term treatment with anticonvulsants (even as adjuvant in pain-relief) may decrease the activation process of VD in the liver. Phenobarbital and phenytoin increase the hepatic metabolism (inactivation) of vitamin D. Corticosteroids inhibit Ca++ absorption, which results in impaired VD metabolism. Thiazide-type diuretics may induce hypercalcemia and subsequent arrhythmia in patients on digitalis therapy. Co-administration with magnesium-containing medicines/dietary supplements (incl. antacids, too) should be also avoided. Since VD is fat soluble, certain drugs affecting the fat absorption (orlistat, cholestyramine) can reduce the intestinal absorption of vitamin D. In contrast: vitamin D supplementation may decrease the serum levels of statins, eg. atorvastatin due to its inductive effect on CYP3A4 by which atorvastatin is partially metabolised. This effect may influence metabolism of a lot of drugs depending on the activity of hepatic isoenzyme CYP3A4, however the reports on this type of interaction are scarce.

Finally, in this age group one should not forget about the adherence to drug administration. Medication failures are more frequent in the elderly especially who live alone, and the missing administration of drugs and/or dietary supplements are also accidental ground of lack of effect [13].

In the elderly, melanin, which is very effective UVB absorber, often decreased in the skin pigmentation, thus the dermic synthesis of VD is also reduced. The moderate use of modern sunscreens does not inhibit the vitamin D synthesis in the epidermis, in contrast to strict physical avoidance of sunlight [14,15]. In contrast creams of the older generation (main ingredient: para-aminobenzoic acid) with sun protection factor 30 reduced VD synthesis in the skin by more than 95%, according to an assessment of 1987 [16]. To avoid increased risk of HypoVD, there have been developed reliable self-administered VD status predictors that can used by older patient as well [17].

Interestingly, Gorter et al. [18] published some years ago that along with the often referred risk factors (elevated age, non-Caucasian skin type, winter; smoking) main protective factors against severe vitamin D deficiency are VD supplementation, higher daily sun exposure and the regular alcohol consumption. The last one, of course, does not cover the uncontrolled drinking habit.

Hypovitaminosis D in the Obese

Duré-Travé and co-workers published a survey of 564 young (3,6-15,8 yo) Caucasian individuals in Spain and revealed that prevalence of hypovitaminosis D (HypoVD) was extra high (81,1%) in severe obese and high (68,2%) in obese [19]. In contrast, HypoVD was present in the half of individuals having normal (58,1%) or overweight (55%). Numerous studies with old participants support the inverse association of se-25-OH-D and BMI greater than 30 kg/m² thus obesity is irrespective of age associated with VD deficiency, however, the causative role of HypoVD in development of obesity is still not proven. Obese people in general, show also higher serum PTH level than healthy weight people. As known, PTH levels are inversely associated with vitamin D levels and patients with hyperparathyroidism are on average more obese than eparathyroid population [20].

The elevated potency of adipose tissue to store VD has long been known but only recent studies revealed that vitamin D receptors and vitamin D metabolizing enzymes are expressed in adipocytes as well. By this presence VD influence the regulation of adipogenic gene expression incl. lipogenesis and lipolysis, cytokine release, NF-kB signaling (low grade inflammation process), etc. has been demonstrated [21]. Thus, the relation between VD status and obesity-beyond the storage of this fat-soluble vitamin is not just a hypothesis anymore.

Vitamin D also affects the appetite regulation through the leptin-production and the carbohydrate metabolism via influencing insulin-sensitizing hormone release. There are many hypotheses about the details of HypoVD link with overweight/obesity. One of them is that low serum 25-OH-vitamin D levels block leptin and increase adiponectin release therefore these adipokines levels facilitate fat deposition. The opposite situation has also been proved: in a study 32 patients received weekly 50000 IU vitamin D and the leptin level moderately increased, the adiponectin level moderately decreased in comparison to 32 control patients of the similar mean age (62 and 60 years, respectively) [22].

Clinical studies in this field are, unfortunately, heterogenous. Analysis of observational studies and randomized controlled trials (RCTs) present controversial picture: observational studies supported the inverse association between leptin and 25-OH-VD but RCTs failed to support this result [23].

More and more obese patients choose the surgical solution. Bariatric surgery does not reverse the vitamin D deficiency of obesity, rather such surgery makes HypoVD worse due to the limited absorption surface.

Thus, the relation between obesity and HypoVD is ambiguous and results off small studies are not supported with high value randomized clinical trials. VD supplementation may prevent obesity, but it does not lead to weight loss in obese subjects. It is, however, clear that due to the high distribution potential of VD in the adipose tissue, a large amount of VD disappears from the circulation therefore supplementation with higher doses is necessary if VD deficiency is verified.

The D-Hypervitaminosis

Due to an inborn defence mechanism if active VD (1,25-dihydroxycholecalciferol) is sufficient, the molecule is further metabolized by CYP24 enzymes in the liver and the kidney (Figure 3). These metabolites are already inactive. Besides and among other regulatory factors, the activation step 25-OH-D3 to 1,25(OH)2D3 is age dependent, ie. in the elderly production rate of calcitriol is diminished [24].

Even so, rarely and mostly in the early childhood, D-hypervitaminosis may occur. This is usually due to inborn error the hydroxylation of cholecalciferol and it results in extreme high se-levels of 25-OH-vitamin D. In the adults, this kind of toxicosis may not come true because even in high 25-OH-VD levels 1,25-dihydroxy-VD is relatively low. The regulator is the hydroxylation process in the kidney and the difference of intracellular receptor-affinity: VD-nuclear receptor affinity to calcitriol is 1000-fold of 25-OH-VD. Moreover, the affinity of plasma transport-proteins is ca. 200x higher of 25-OH-VD than that of calcitriol thus overdosing of VD can hardly reach as high concentration that would evoke adverse effects. Moreover, according to a study with 38 patients, 10 000 IU vitamin D per day for 4 months resulted in no adverse effects, it means vitamin D has a wide therapeutic window [25]. In very rare cases and in very high doses (eg. overdosage of supplements or medical [iatrogenic] inter
Vitamin D deficiency is a relative phenomenon, depending on the definition of threshold. Due to the wide range of risk factors leading to HypoVD, many individuals need correction in vitamin D status. Maybe the non-pharmaceutical options of correction are present or probable, administration of vitamin D supplementation is recommended. The therapeutic amount should be fitted to the degree of deficit; without laboratory measurement 800-1200 IU per day advisable for elderly above 70 years and for obese individuals above 30 kg/m².

REFERENCES


