Chapter

Vitamin D in Elderly

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Abstract

Vitamin D deficiency is common in elderly people, especially in patients with comorbidity and polypharmcy. In this group, low vitamin D plasma concentration is related to osteoporosis, osteomalacia, sarcopenia and myalgia. Vitamin D status in geriatric population is an effect of joint interaction of all vitamin D metabolic pathways, aging processes and multimorbidity. Therefore, all factors interfering with individual metabolic stages may affect 25-hydroxyvitamin D plasma concentration. The known factors affecting vitamin D metabolism interfere with cytochrome CYP3A4 activity. The phenomenon of drugs and vitamin D interactions is observed first and foremost in patients with comorbidity. This is a typical example of the situation where a lack of "hard evidence" is not synonymous with the possible lack of adverse effects. Geriatric giants, such as sarcopenia (progressive and generalized loss of skeletal muscle mass and strength) or cognitive decline, strongly influence elderly patients. Sarcopenia is one of the musculoskeletal consequences of hypovitaminosis D. These consequences are related to a higher risk of adverse outcomes, such as fracture, physical disability, a poor quality of life and death. This can lead not only to an increased risk of falls and fractures, but is also one of the main causes of frailty syndrome in the aging population. Generally, Vitamin D plasma concentration is significantly lower in participants with osteoporosis and muscle deterioration. In some observational and uncontrolled treatment studies, vitamin D supplementation led to a reduction of proximal myopathy and muscle pain. The most positive results were found in subjects with severe vitamin D deficiency and in patients avoiding high doses of vitamin D. However, the role of vitamin D in muscle pathologies is not clear and research has provided conflicting results. This is most likely due to the heterogeneity of the subjects, vitamin D doses and environmental factors.

Keywords: Vitamin D, pleiotropic effect, elderly, aging

1. Introduction

Vitamin D is a fat-soluble vitamin mainly produced by the skin after sun exposure (cholecalciferol - vitamin D3) and can also be obtained from food (ergocalciferol-vitamin D2 and vitamin D3) or supplementation. In the liver, vitamin D (the term "vitamin D" refers both vit.D2 and vit.D3") is converted to 25-hydroxyvitamin D [25(OH)D]), also known as "calcidiol", the major circulating metabolite of vitamin D which can be measured in the blood. In the kidney, [25(OH)D] is converted by 1-alfa-hydroxylase into its active form called 1,25-dihydroxyvitamin D [1,25(OH)2D], also known as "calcitriol", that plays a vital role in maintaining bone

homeostasis by regulating calcium metabolism. This action of [1,25(OH)2D] is referred to as endocrine action. The other area where [25(OH)D] is converted by peripheral 1-alfa-hydroxylase to [1,25(OH)2D] are cells in various tissues. There, [1,25(OH)2D] regulation by autocrine or paracrine actions have been observed.

Vitamin D deficiency and insufficiency is one of the major world-wide health problems and its consequences seem to be more serious in the elderly population than in younger adults. It has been associated with a wide range of diseases including autoimmune diseases (among others multiple sclerosis, type 1 diabetes, rheumatoid arthritis), cardiovascular diseases (for example stroke), infectious diseases (bacterial, viral and, fungal), type 2 diabetes and some types of cancers (colorectal, breast and prostate gland). It is also recognized that vitamin D deficiency is associated with some psychiatric disorders including depression, neurocognitive dysfunction and others forms of neurodegenerative disorders (Alzheimer's disease) [1].

This recognition has not only resulted in broadening our knowledge and more conscious vitamin D prescriptions but also led to the crucial question in everyday clinical practice: How can we use our knowledge to improve care for elderly people with vitamin D deficiency and to guide future research studies? Therefore, our publication is focused on distinctive characteristics of vitamin D metabolism, deficiency and drug interaction in the elderly population. As the range of aspects of vitamin D effects in the geriatric population is extremely wide, only chosen elements typical for elderly patients could be presented to emphasise the complexity of the issue.

2. Vitamin D deficiency in the aging population

Available data indicates that in many countries all over the world, the general population (irrespective of the latitude of residence, age, sex and race) and patients considered as otherwise healthy, suffer from vitamin D insufficiency, defined as 25(OH)D < 30 ng/ml. Recent large observational data have suggested that ~40% of Europeans are vitamin D deficient, and 13% are severely deficient [2]. When 25-hydroxyvitamin D levels were analyzed in relation to age (based on 10-year ranges) there were significant differences in the level of 25(OH)D. The level of 25(OH) D was significantly lower in the older population. However, there are conflicting data concerning the subject, for example in a large Japanese study, the adjusted odds ratio for circulating 25OHD > 75 nmol/l (>30 ng/ml) was in men and women aged >70 years (reference group: individuals aged <50 years) 2.55 and 2.26, respectively. In Bergman et all study, patients aged over 65 years had significant lower circulating 25OHD levels than patients over 75 years [3–6].

3. Elderly people are not a homogenic population

Meanwhile, the elderly and the oldest-old are one of the fastest growing populations all over the world. The number of people aged 65 and older is expected to rapidly increase in the next decades. Not only the elderly, but also the oldest old are still increasing in numbers. Globally, the current average annual growth rate of people aged 80 years or older (3.8 per cent) is twice as high as the growth rate of the persons younger than 60 years of age (1.9 per cent) [7]. Despite the same range of biological age, it is not a homogenic population regarding the aging type (successful or unsuccessful). Multimorbidity combined with polypharmacy is common, so functional assessment and mobility determine the quality of life. The role of vitamin D in the prevention and treatment of diseases associated with aging

is still being researched. Therefore, during last decade, geriatric medicine has been focused on studies concerning not only vitamin D deficiency in elderly, but especially on its possible impact on Healthy life years (HLY, also called disability-free life expectancy) taking into account the role of vitamin D considered as a potential factor strongly influencing possible elongation of HLY. Vitamin D status has been widely studied in the last decade. Undoubtedly, one of the most important clinical question concerns the possibilities of preventing of unhealthy aging.

4. Factors contributing to vitamin D deficiency in the elderly

Most importantly, [1,25(OH)2D] directly or indirectly regulates over 200 genes including those involved in: rennin production in the kidney, insulin in the pancreas, the release of cytokines from lymphocytes, production of cathelicidin by macrophages, and the growth and proliferation smooth muscle cells and cardiomyocytes. The main cause of aging-associated vitamin D deficiency is low vitamin D production. As we age, there is a reduction in the skin's concentration of 7-dehydrocholesterol [8]. Specifically, for each decade past the age of 40, there is approximately a 10 to 15% decrease in the level of 7-dehydrocholesterol. Furthermore, the character of dressing style makes the sun exposure indispensable as well as short time of outdoor activities, taking into account that a sufficient amount of sunlight radiation for vitamin D production by the skin only occurs between May and September in some latitudes. Additionally, there is about a 35% decrease in intestinal calcium absorption after the age of 70 [9]. This decrease is even greater in women because of reduced fractional calcium absorption and estrogen changes after the menopause with increased urinary calcium losses [10]. Other causes of aging-associated vitamin D deficiency are related to poor vitamin D and calcium nutrition. With age, comorbidity must also be taken into account with a special focus on renal and liver insufficiency.

5. Vitamin D and geriatric giants

With advanced age, people appear to change their health status perception as a range of independence rather than lack of disease. The presence of "geriatric giants" (coined by Bernard Isaacs in 1965 to encompass common impairments) contributes to more serious consequences than in younger groups [11–13]. Recent epidemiological research has shown that the concentration of 25-hydroxyvitamin D may have an impact on various age-related diseases, as well as on geriatric giants. Geriatric giants are common, have multiple contributing factors and their consequences are stronger in older groups of patients. Some geriatric giants, like sarcopenia, falls or cognitive decline, neurodegenerative disease, and depression are likely to have extremely strong impact on independency of individuals and high risk of negative outcomes.

5.1 Sarcopenia

Sarcopenia is known as a new geriatric giant. It is an interdisciplinary and multifactor symptom whose prevalence rises with age. Furthermore, the development of secondary hyperparathyroidism favors a negative calcium balance, high bone turnover and accelerates age-related bone loss and osteoporotic fractures.

According to the consensus of The European Working Group on Sarcopenia in Older People, the diagnosis is based on three criteria: low muscle strength or/and

low physical performance, and low muscle mass. Sarcopenia is a progressive process and, as a new geriatric giant, has many contributing factors - not only the aging processes, but also vitamin D deficiency, diet, sedentary lifestyle, diseases, drug treatments and drug interactions [14].

Sarcopenia has strong impact on the outcomes of the risk of falls and osteoporotic fractures, lack of independency and lack of ability to perform activities of daily living. Subjects with sarcopenic obesity in the MrOS study had a 1.9 increased risk of any fracture and 3.1 increased risk of spine fracture [15]. The loss of strength is also an important criteria for a diagnosis of frailty syndrome (FS). Therefore, sarcopenia associated with muscle loss in frailty syndrome is one of the major issues of geriatric medicine. The prevalence of frailty syndrome is growing with age. The key role that vitamin D plays in muscle function and low muscle strength has been described in subjects with osteomalacia. The effects of 1,25(OH)D on the proliferation and differentiation in myogenic cells have also been described [20]. Although it remains highly debated, the action of vitamin D via the VDR receptor seems to play a significant role in muscle development and growth [16–18].

It remains unclear in observational studies if there is a key role in vitamin D interaction with muscle, or rather this is the effect of other factors. In an eight-year longitudinal study, the supplementation of vitamin D was not associated with a decreased risk of frailty, but the average daily dosage of oral vitamin D was lower than 400 IU and probably not enough to achieve the target of serum 25(0H) D concentration of 20 ng/ml. Additionally, the lowest 25(OH)D season-specific quartile correlated with a faster rate of muscle strength loss in men aged over 85 [19, 20]. The process was observed in all subjects, including those who were not supplemented with vitamin D. Some interventional studies have been conducted to describe the role of vitamin D in musculosceletal health. However, only a few of these studies had muscle strength as the endpoint. Vitamin D may affect muscle function, particularly in vulnerable populations such as the oldest old and patients with severe sarcopenia. However, it is difficult to create a homogenic group of subjects with the oldest old due to a large number of cofactors that influence physical performance. Nevertheless, vitamin D supplementation for preventing sarcopenia still requires a controlled, double–blind research design.

Sarcopenia being one of the crucial factors of frailty syndrome constitution provides a significant increase in falls that are one of the many causes of disability and functional decline in elderly people. Despite numerous trials and meta-analyses conducted the efficacy of vitamin D supplementation as a mean to prevent falls remains uncertain. The effectiveness of vitamin D in fall prevention remains an issue of the debate. Authors of publications have underscored the importance of further trials on vitamin D and falls and highlight 3 key characteristics these trials should comprise: vitamin D deficiency, vitamin D administration, and unified falls documentation [21].

5.2 Cognitive decline: dementia, depression

Vitamin D, by direct and indirect regulation of more than 200 genes, exerts bioactivity as a hormone and plays an important role in processes important for the functioning of all systems as well as central nervous system, including calcium absorption, tissue and immune cell growth, and inflammation. However, the crucial role of vitamin D for brain health is supported by the presence of the enzyme that produces its active form 1-hydroxylase in cerebrospinal fluid. The receptor for the active metabolite is found throughout the human brain. Vitamin D has been linked with neuron growth and survival by its regulation of factors such as glutathione, growth factors, neurotrophies and neurotransmitters. Moreover, in animal

models, vitamin D supplementation showed reduced inflammatory biomarkers in the hippocampus. Vitamin D receptor (VDR) seems to be one of the most probable genetic factors of Alzheimer disease (AD). VDR polymorphism increases the risk of AD by 2.3 times and in molecular studies, vitamin D treatment prevented amyloid production and enhanced its removal [22].

The pleiotropic aspects of vitamin D action was tested in numerous observational studies suggesting an association between low serum concentration and the increased risk of other geriatric giants such as cognitive decline, dementia and depression and its supplementation has also shown an improvement in the cognitive performance in elderly patients with senile dementia.

5.2.1 Epidemiological studies

A survey was conducted in Norway among patients over 65 years old with depression who were admitted to psychiatric wards. Vitamin D deficiency (below 20 ng/ml) was observed in 71% patients with depression, 50% patients with bipolar affective disorder and in 25% of control group patients. However, in other studies, there exist a wide range of differences between vitamin D deficiency status (from 34,6% in USA to 100% in British research). Because of the existing conflicts in the data, Li et all in 2018 conducted a meta-analysis to extend the knowledge concerning vitamin D deficiency in patients with depression. They assumed that for every 10 ng/ml of vitamin D level, the increase risk of depression decreases 12%. So, vitamin D supplementation could be useful in the reduction of depression risk, but until this time, the data of RCT's are not conclusive [23, 24].

5.2.2 Alzheimer's disease (AD)

Two meta-analysis underscored significantly lower vitamin D concentrations in patients with AD compared to healthy individuals. The risk of AD in patients with vitamin D deficiency was found to be twice higher in an American study and 2.85 times higher in a French study. There exists a correlation between the stage of deficiency and concentration - respectively 19% for concentration below 20 ng/ml and 31% for severe deficiency (<10 ng/ml). However, concentrations >35 ng/ml were not correlated with a of lower risk of AD. Vitamin D pretends to be an independent protective factor reducing Alzheimer diseases processes. For example, in a Spanish study, the dynamics of Alzheimer disease was slower in patients receiving vitamin D. However, the data concerning influence of vitamin D supplementation in AD remains not conclusive [25, 26]. There is also lack of prospective RCT studies.

6. Comorbidity and infections

Notably, several studies have reported an inverse association between 25(OH)D serum levels and the risk of infections (including oral, gastrointestinal, urinary, and respiratory). Many studies underscored the potential immunomodulatory effects as well as the association between the low serum vitamin D levels and many other diseases, such as endocrinal dysfunction leading to increasing insulin resistance, diabetic negative outcomes (for example retinopathy), and cardiovascular disorders. Therefore, all those elements of diseases, typical for elderly patients, create unfavourable background for constitution and progression of geriatric giants. However, in a Lithuanian cross-sectional study (Alekna et al.) of serum 25(OH)D concentrations in relation to activities of daily living (ADL) conducted among octogenarians the regression coefficient for 25(OH)D concentration vs. ADL category

was 0.2 (p = 0.01). As highlighted by the authors, it was impossible in this study to determine whether ADL status was a cause or an effect of serum 25(OH)D concentration [27] Complexity of aging processes, age related diseases, geriatric giants and socioeconomic factors influencing elderly patients result in multifactorial, elaborate relation between all this factors to vitamin D status.

The last several months have strongly influenced geriatric medicine. COVID infection has become a clinical example of how important the role of vitamin D is in immunomodulation and anti-inflammatory effect for organisms in particular of aging organs.

7. Vitamin D supplementation and vitamin D treatment in elderly

7.1 Recommendations for general elderly populations

Recommendations for vitamin D intake in asymptomatic healthy individuals and in asymptomatic healthy individuals at high risk of vitamin D deficiency (which was published as the Central European Recommendation; similar to the Endocrine Society in USA) are presented in **Tables 1** and **2**. These guidelines recommend the use of vitamin D supplements to obtain and maintain the optimal target 25(OH)D concentration in range of 30-50 ng/ml (75-125 nmol/m).

As presented in **Tables 1** and **2**, people over the age of 65 should take 800- 2000 IU/d of vitamin D throughout the whole year, but people younger than 65 should take vitamin D in the same doses only when the photosynthesis in the skin is insufficient, during the winter months at latitude of >40°, little or no UVB radiation reaches the surface of the earth; such as in Poland from October to March (**Table 1**). The recommended vitamin D intake for groups at risk of vitamin D deficiency and requires larger doses of vitamin D (**Table 2**). This includes night-time workers and dark-skinned people (1000-2000 IU/d of vitamin D for the whole year) and obese people (1600 IU/d to 4000 IU/d for the whole year). There are two essential points about supplementation in the healthy population. First, measurements of [25(OH)D] should not be tested before and during supplementation and second, vitamin D doses larger than the tolerable upper intake levels (ULS) to prevent deficiency of vitamin should not be prescribed. The ULS for adults and seniors with normal body weight is 4000 IU/d, but in obese adults and seniors, it is higher (10 000 IU/d.) [28].

It is very important that treatment of vitamin D deficiency is based on 25(OH) D concentration and antecedent prophylactic management. Individual patients with serum 25(OH) < 20 ng/ml that have clinical risk factors for vitamin D deficiency (decreased intake, gastrointestinal diseases, chronic hepatic diseases, renal diseases, medication with antiepileptic drugs and others which disturbing metabolism of vitamin D) with bone diseases (fragility fractures, documented osteoporosis or

		Sufficient skin synthesis		Supplementaion vitamin D IU	
Season in year		**October–March**	**April–September**	**October–March**	**April-September**
Adults	to 65 years	—	+	800-2000	—
	after 65 years	—	—	800-2000	
Recommendation: do not routinely test 25 (OH)D levels in these groups					

Table 1.
Recommended vitamin D intake in asymptomatic healthy individuals at high risk of vitamin D deficiency.

		Sufficient skin synthesis		Supplementaion vitamin D IU	
Season in year		**October–March**	**April–September**	**October–March**	**April–September**
Adults	Nighttime workers	—	—	1000-2000	
	Dark-skinned	—	—	1000-20000	
	Obese (adults and seniors)	—	—	1600-4000	
Recommendation: do not routinely test 25 (OH)D levels in these groups					

Table 2.
Recommended treatment for individual patients with vitamin D deficiency.

high fracture risk, treated with antiresorptive medication, osteomalacia) should be treated. The primary treatment objectives for vitamin D deficiency are the prescription of adequate doses to ensure correction of vitamin D deficiency (>20 ng/ml), reversing the clinical consequences of vitamin D in a timely manner and avoiding toxicity.

The oral route (intake) of treatment is recommended (vitamin D2 and vitamin D3) and should be taken with food to aid absorption. The dosage should be adjusted on the basis of the baseline deficit and the patient's weight (schematic representation for elderly population presented below in the **Figure 1**). The control level of [25(OH)D] should be attained during treatment at the beginning and after 7-10 weeks.

Treatment of vitamin D deficiency should consist of 2 parts: the initial repletion phase of therapy (loading phase), and after the loading phase, initiating the maintenance.

The loading phase with vitamin D requires 7 to 10 weeks. The aim is to saturate all body compartments so the level of [25(OH)D] is above 30 ng/ml (75 nnom/l. During this time, loading doses of vitamin D (about 300 000 IU) should be given as daily split (divide) doses or intermittent doses every week. Single mega doses (300 000 IU to treat deficiency) are not recommended in the treatment of vitamin D deficiency. Maintenance regiments may be considered after the loading doses.

Example regiments: all loading doses are 300 000 IU and may by administered by a weekly or daily split.

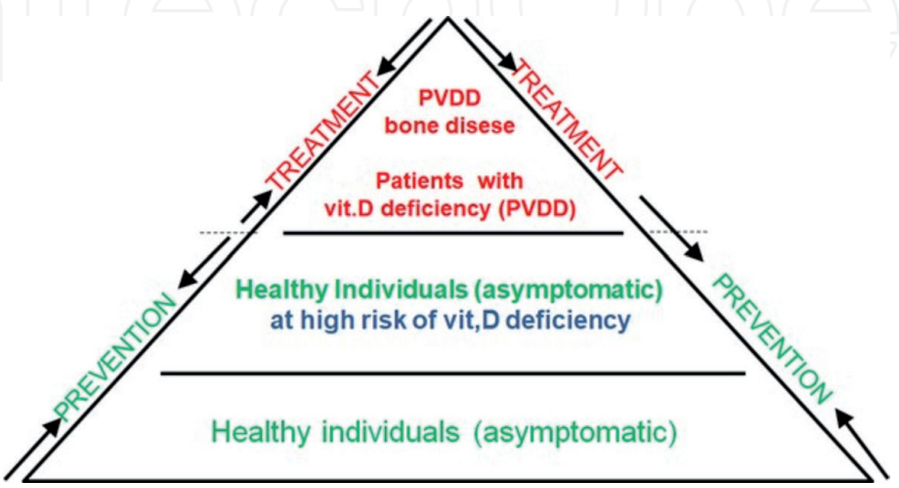

Figure 1.
Schematic representation elderly population vulnerable to vitamin D deficiency that defines broad groups for clinical consideration and decision-making about supplementation or treatment with vitamin D elderly individuals' (PVDD – patients with vitamin D deficiency).

50 000 IU capsules, one given weekly for 6 weeks.
20 000 IU capsules, two given weekly for 7 weeks.
1000 IU capsules, 4 a day for 10 weeks.

Maintenance regiments after loading doses (given either daily (800 – 4000 IU/D) or intermittently at higher equivalent doses (20 000 every 2 weeks).

The rapid correction of vitamin D deficiency may be necessary in some patients. Rapid correction is required in patients with symptomatic disease or those about to start treatment with potent antiresorptive agent, such as zolenndronate or denosumab. In these cases, the recommended treatment is based on split-loading doses (not single large doses) followed by regular maintenance therapy. Regarding the differences between cholecalciferol and calcifediol, including faster intestine absorption of the calcifediol and linear increment uninfluenced by baseline vitamin D level, in elderly patients often this type of therapy should be considered.

Less urgent correction with lower subsequent dosing is required in patients with increased sensitivity to vitamin D therapy because of genetic abnormality in vitamin D metabolism, co-morbidities such as CD, granulomatoforming diseases or hyperparathyreoidismus [29, 30] .

Analogs 1 alfa (OH)D, 1, alfa 25(0H2)D and others should not be used in therapy of vitamin D deficiency or insufficiency. It is worth of mentioning that in the elderly patients, presence of geriatric giants, multimorbidity and drug interactions should be taken into account.

8. Vitamin D intake and polypharmacy

The problem of polypharmacy and drug interaction is common in geriatric patients, as multimorbidity is a typical characteristic of this population. This makes it necessary to take into account assumptions concerning the possible interferences of widely used drugs on vitamin D metabolism. Vitamin D status in humans is an effect of the joint interaction of all vitamin D metabolic pathways. Therefore, all factors that interfere with individual metabolic stages may affect 25-hydroxyvitamin D concentration in the circulation. To date, there is little hard evidence that agents such as lipase inhibitors, statins, antimicrobials, antiepileptics and others affect [25(OH)D] concentration in blood serum. The issue of drug and vitamin D interactions is a clear example of a situation where lack of evidence does not equate to “no harm”.

The agents with a potential to influence vitamin D status can be roughly divided into drugs that effect vitamin D intestinal absorption and those that influence vitamin D metabolism [31].

Included in the first category, lipase inhibitors are widely used for obesity treatment. They decrease triglycerides hydrolysis in the gut, causing an incremental rise of excreted fat from the typical 5% up to 30%. This increases fat-soluble vitamin D loss in the feces, at the same time decreasing the vitamin D pool available for absorption in the small intestine. In the second category of drugs that influence vitamin D metabolism, statins are an important class and are widely used as very effective agents in both the primary and secondary prevention of cardiovascular diseases.

Statins are the most widely prescribed cholesterol-lowering drugs in the world, and they are expected to generate a revenue over $1 billion by 2025. All statins function as inhibitors of a rate-limiting enzyme in synthesis of cholesterol, namely hydroxyl-methyl coenzyme A (HMG-CoA) reductase. This action brings statins close to vitamin D metabolism, at the same time suggesting their uniform action and similar side effects. Nevertheless, the results of numerous studies show

that the statins/vitamin D interaction give diverse and pleiotropic results. This is evident by a meta-analysis that was "inconclusive on the effects of statins on vitamin D with conflicting directions from interventional and observational studies". Although the fundamental mechanism of action is identical for all the statins, they differ in water solubility, and are catabolized in different ways depending on the statin type, patient's age and vitamin D status, nutritional conditions and insolation. There are two basic ways of the disposition of statins from the human body. One is degradation of some statins in the stomach and excretion as native compounds, the second is an oxidative pathway where the statins undergo modification by a specific cytochrome P450 isoenzymes resulting in an enhanced solubility and subsequent excretion. Some of those enzymes belong to the CYP3A family, and that is the meeting point of the vitamin D and statins catabolic pathways [32].

It is known that atorvastatin, lovastatin and simvastatin are primarily metabolized by CYP3A4, a multi-substrate cytochrome involved also in vitamin D metabolites catabolism. Cytochromes in the CYP3A category are also very important enzymes in the vitamin D catabolic pathways. Therefore, any interference with their activity may cause a disturbance in the vitamin D status of the patient. It is known that some statins may compete for the active centers of the CYP3A enzymes, slowing down the catabolism of the vitamin D metabolites. This results in the vitamin D status increasing, especially in patients who are supplemented with vitamin D. It has been found that atorvastatin treatment significantly increases 25-hydroxyvitamin D concentration in patient's blood serum. This increase is especially visible in patients treated with 800 IU of vitamin D per day. This effect is probably due to inhibitive competition of vitamin D metabolites and the statin for a limited number of active centers available in CYP3A4, and therefore the decrement of the metabolic clearance of the vitamin D metabolites. There are also reports that statins (e.g., rosuvastatin) that are not metabolized by CYP3A4 correlate with the increased 25OHD concentrations in the circulation system of the patient. There is no simple explanation for this finding. One possibility is that statins may act as inducers of the vitamin D 25-hydroxylase activity expressed to a certain extend by the CYP3A4 [33].

Statins are also known to increase the catabolic clearance of vitamin D metabolites. The mechanism of this phenomenon relays on their affinity for nuclear receptors (PXR, CAR) involved in regulating the expression of CYP3A proteins. [34].

Antiepileptics (AEDs) as carbamazepine, oxcarbazepine, phenobarbital, phenytoin, primidone, and valproate have all been associated with bone health problems in epileptic patients. Taking into account that some of them are prescribed as coanalgesics, this type of therapy is widely use in clinical practice among elderly patients. AEDs are known to induce the enzymes from the catabolic pathway of the vitamin D. This action results in a specific sequence of events leading to an increased fracture risk beginning with the induction of hepatic cytochromes and accelerated degradation of the vitamin D metabolites. AEDs can result in decreased vitamin D status and decreased intestinal calcium absorption that has a negative effect on the circulating calcium pool. In turn, this activates a compensatory increase in PTH concentrations resulting in increased bone resorption and an increased risk of fractures. The negative effects of anticonvulsants on fracture risk were confirmed by a population-based analysis. The study had nearly 16,000 participants who had a nontraumatic fracture of the wrist, hip and vertebra with up to 3 matched controls ("n" around 47,000). A significant increase of fracture risk was found for most of the antiepileptic drugs investigated namely for carbamazepine, clonazepam, gabapentin, phenobarbital and phenytoin. OR values ranged from 1,24 for clonazepam to 1,91 for phenytoin. Valproic acid was the only AED

not associated with increased fracture risk. These results are consistent with other population-based studies [35, 36].

Research was conducted to determine if vitamin D supplementation improves the bone condition in patients taking anti-epileptic drugs. The results of a systematic review of 9 studies reported that the research was marred by very little uniformity with respect to the vitamin D dosing regimen, sample sizes, the antiepileptic drugs used, study length and design and bone outcomes measured. Nevertheless, the review states that vitamin D supplementation seems to have a positive effect on bone turnover markers, especially alkaline phosphatase and bone mineralization in adults with epilepsy.

The mechanisms of action and observational data suggest that other factors might interfere with the metabolism of vitamin D. This group comprises of glucocorticoids, immunosuppressive agents (cyclosporine, tacrolimus), many chemotherapeutic agents, highly active antiretroviral agents, and histamine H2-receptor antagonists.

Glucocorticoids belong to a widely used class of drugs. Prednisone, hydrocortisone, dexamethasone are used in adrenal replacement, immune suppression and chemotherapy. The well-known side-effect of their application is osteoporosis. Therefore, alterations in vitamin D metabolism have been investigated as a possible mechanism. It has been found that glucocorticoids induce several P450 cytochromes in a way similar to AED, including the vitamin D catabolizing CYP2A4. Although the RCT class studied failed to produce conclusive results, a recent overview of systematic literature revealed that the prevalence range of fractures or osteoporosis in patients taking glucocorticoids is 21 to 30%. The postulated remedy for these problems, save for decreasing the glucocorticoids dose, is vitamin D supplementation [37, 38].

9. Other drugs

One of published metanalysis underscored undoubted need for further research to understand the impact of drugs that inhibit CYP enzyme activity related to vitamin D status. Regarding such treatment as the antimicrobial agent ketoconazole or proton pump inhibitor omeprazole, have been shown to inhibit both CYP3A4 166, 167 and CYP24 168 in vitro, so far, no studies have evaluated the clinical effect of these drugs on human vitamin D status in elderly [39].

10. Vitamin D toxicity in elderly

Vitamin D toxicity (VDT) due to excess of vitamin D is a clinical condition characterized by severe hypercalcemia that may persist for a prolonged period of time and lead to serious health consequences. Hypervitaminosis D with hypercalcemia develops after uncontrolled use of vitamin D mega doses or vitamin D metabolites [25(OH)D, 1,25(OH)2D]. Hypervitaminosis D may develop in some clinical conditions as a result of using vitamin D analogs (exogenous VDT). Hypervitaminosis D with hypercalcemia may also be a manifestation of excessive production of 1,25(OH)2D in granulomatous disorders such as sarcoidosis, tuberculosis, leprosy, fungal diseases, giant cell polymyositis, and berylliosis. In healthy geriatric population, exogenous vitamin D toxicity may be caused by prolonged use (months) of vitamin D mega doses, but not by the abnormally high exposure of skin to the sun or by eating a diversified diet. Exogenous VDT due to vitamin D overdosing is diagnosed in the elderly similar as in younger people (very rare) by

markedly elevated 25(OH)D concentrations (>150 ng/ml) accompanied by severe hypercalcemia and hypercalciuria and by very low or undetectable parathyroid hormone (PTH) activity [40, 41].

Exogenous VDT can be the result of patients taking excessive amounts of 1,25(OH)2D or other 1–hydroxylated vitamin D analogs [1(OH)D], for example paricalcitol and doxercalciferol, used to treat hypercalcemic disorders, including hypoparathyroidism, pseudohypoparathyroidism, osteomalacia, and end- stage renal failure. When this occurs, hypercalcemia is a harmful side effect of treatment with a pharmacological vitamin D agent that is not related to 25(OH)D concentration and when the concentration value of 1,25(OH)2D is elevated. The increased risk of endogenous VDT is a serious clinical issue in the elderly with granuloma-forming disorders and in lymphomas. Patients with granuloma-forming disorders and lymphomas are hypersensitive to vitamin D. Elevated 1,25(OH)2D concentration with hypercalcemia may develop after vitamin D supplementation, from dietary products fortified with vitamin D or after sunbathing. In granulomatous diseases (including tuberculosis, sarcoidosis, leprosy, fungal diseases, infantile subcutaneous fat necrosis, giant cell polymyositis, and berylliosis) endogenous VDT is related to the abnormal extrarenal synthesis of 1,25(OH)2D by activated macrophages. In lymphomas, the etiology of VDT is multiple, heterogeneous, and still not fully recognized. In endogenous VDT, hypercalcemia is related to increased 1,25(OH)2D concentration. In contrast, hypercalcemia is a consequence of high 25(OH)D concentration due to an overdose of vitamin D (exogenous VDT) [42, 43].

Over the last decade, the Institute of Medicine (IOM) and the Endocrine Society have both concluded that acute VDT is extremely rare in the literature, that serum 25(OH)D concentrations must exceed 150 ng/ml (375 nmol/l). Other considerations, such as calcium intake, can have an effect the risk of hypercalcemia and VDT. Despite of the risk factors associated with VDT, there is empirical evidence that vitamin D is among the least toxic fat-soluble vitamins, and significantly less toxic than vitamin A. Dudenkov and colleagues researched more than 20,000 serum 25(OH)D measurements performed at the Mayo Clinic from 2002 to 2011 to determine the prevalence of VDT, demonstrated by the presence of hypercalcemia. The number of individuals with a serum 25(OH)D concentration > 50 ng/ml (>75 nmol/l) had increased by 20 times during that period. On the other hand, high 25(OH)D concentrations can coincide with normal concentrations of serum calcium. In this study, only one patient was diagnosed with hypercalcemia with a 25(OH)D concentration of 364 ng/ml (910 nmol/l). Pietras and colleagues [16] reported no evidence of VDT in healthy adults in a clinical setting who received 50,000 IU of vitamin D2 once every 2 weeks (equivalent to approximately 3,300 IU/day) for up to 6 years. These patients maintained 25(OH)D concentrations of 40–60 ng/ml (100–150 nmol/l). Ekwaru and colleagues had similar findings of no evidence of toxicity in Canadian adults who received up to 20,000 IU of vitamin D3 per day and had a significant increase of 25(OH)D concentrations, up to 60 ng/ml (150 nmol/l) [44–47].

11. Conclusions

The world-wide prevalence of vitamin D deficiency and its role in the maintenance of skeletal and non-skeletal health calls for continuing investigation of vitamin D. These actions should take into account a multitude of confounding variables, including age – elderly as well as the oldest-old, presence of geriatric giants and their consequences, evaluation of vitamin D deficiency as symptomatic or asymptomatic, distinction between the need of supplementation or treatment,

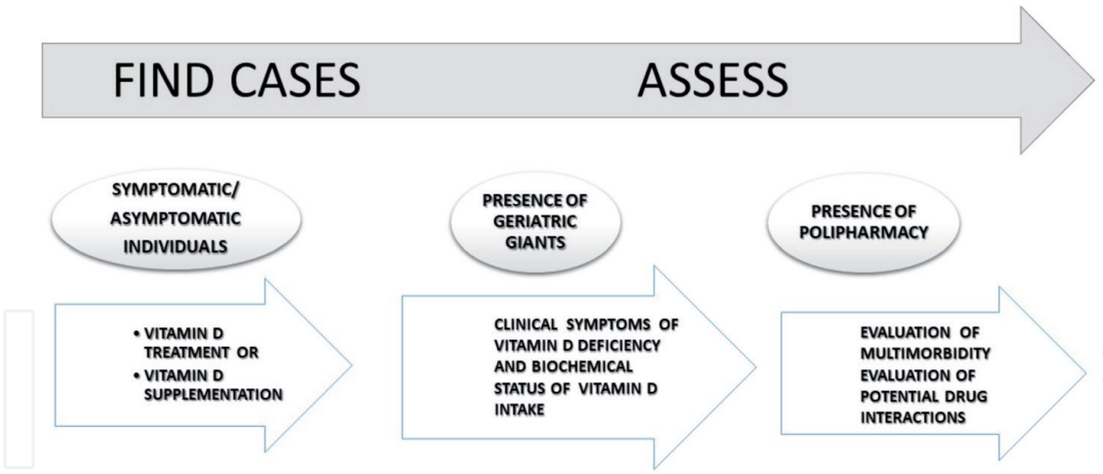

Figure 2.
Proposed strategy for geriatric patient with vitamin D deficiency.

the way of supplementation/treatment, polypharmacy and potential drug interactions. All these factors lead us to define the broad groups for clinical consideration and decision-making regarding the supplementation or treatment with vitamin D in elderly individuals. Heterogeneity of the elderly population contributes to making impossible the creation one, simple algorithm for every patient.

Therefore, the proposed strategy (presented above in the **Figure 2**) to prevent vitamin D deficiency and the negative outcomes in the general elderly population in everyday clinical practice, takes into account multifactorial character of geriatric patient.

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