

Vitamin D deficiency in elderly: Risk factors and drugs impact on vitamin D status

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ABSTRACT

Introduction: Vitamin D (VD) deficiency is a major public health problem worldwide. In spite of its high prevalence, particularly among elderly people, VD deficiency is still underestimated by many physicians. Increasingly, VD deficiency is associated with several known geriatric syndromes. **Methods:** The study sample consisted of 125 patients, aged 75 years and older, admitted to the acute geriatric unit. The plausible association between the serum 25-hydroxyvitamin D [25(OH)D] level and patient age, sex, body mass index, renal function, cholecystectomy history, and the prescribed drugs had been investigated. The Fisher's exact test was used to conduct the statistical analysis of data. **Results:** Surprisingly, furosemide treatment was correlated with normal 25(OH)D levels and an increased incidence of secondary hyperparathyroidism. Unlike the other four parameters mentioned above, our data showed that only the patient sex exhibited a significant association with 25(OH)D level as elderly males suffered from a serious VD deficiency as compared to elderly females. **Conclusion:** Old age is an independent risk factor for VD deficiency. The supplementary dose of VD should be precisely defined to achieve the optimal serum 25(OH)D level in elderly people. The definition of the normal serum 25(OH)D threshold in elderly furosemide-treated patients is worth of further studies.

Key words: Furosemide, geriatrics, Vitamin D deficiency

INTRODUCTION

Vitamin D (VD) or calciferol, a fat-soluble vitamin,^[1] is chemically classified as a steroid.^[2] There are two main sources of VD: the dietary and the endogenous synthesis. Vitamin D₂ (ergocalciferol) is obtained from plants. While a small quantity of Vitamin D₃ (cholecalciferol) is provided by animal-derived food, the main natural VD source is skin synthesis during sunlight exposure (exposure to ultraviolet B).^[3-5] Regardless of its source, VD is hydroxylated in the liver to 25-hydroxyvitamin D [25(OH)D]. 25(OH)D is then converted in the kidneys to its active form, namely 1,25-dihydroxyvitamin D [1,25(OH)₂D]. Serum 25(OH)D level is often seen as a reflection of the total VD status.^[6]

VD plays a crucial role in blood calcium and phosphate homeostasis supporting the body's metabolic functions,

neuromuscular transmission, and bone mineralization.^[7] Furthermore, VD supplementation accelerates fracture-healing rates and decreases the risk of bone fracture.^[8] In regard to the elderly, a direct association between low 25(OH)D levels and frailty syndrome has recently been reported.^[9]

It is worth mentioning, here, that VD also has noncalcemic and nonskeletal effects. Several studies have reported an inverse association between VD levels and the risk of oral, gastrointestinal, urinary, ocular, and respiratory infections. In addition, VD is widely known for its potent

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immunomodulatory role since a strong relationship between VD deficiency and the prevalence of autoimmune disorders was observed.^[10] Other experimental and clinical studies have underscored the association between VD status and some neurological functions in human and animal models. Indeed, it has been reported that obese rats treated with VD supplementation showed a reduced inflammatory biomarkers in the hippocampus.^[11] Moreover, VD supplementation has also shown a significant improvement in the cognitive performance in elderly patients with senile dementia.^[12] VD deficiency affects the endocrinal function as it leads to increasing insulin resistance and an alteration in pancreatic β -cell function.^[13] Furthermore, VD supplementation decreases the fasting blood glucose in type 2 diabetic patients.^[14] Several clinical and epidemiological studies have highlighted the association between VD deficiency and various cardiovascular disorders, such as coronary artery disease, high blood pressure, congestive heart failure, peripheral arterial occlusive disease, stroke, and subarachnoid hemorrhage.^[15-22] Furthermore, many studies underscored the association between the low serum VD levels and many other diseases such as diabetic retinopathy, migraine, bladder carcinoma, and colorectal cancer.^[23-26]

Although these documented associations between VD deficiency and prevalence of many disorders prevalence have been noted, the available studies conducted on the VD supplementation therapeutic effects have resulted in paradoxical data raising the need for further preclinical, epidemiological, and clinical studies to puzzle out the complex therapeutic benefits of VD.^[10]

VD deficiency is a pandemic nutritional problem throughout the world.^[27-31] Interestingly, VD deficiency has been reported even in some equatorial countries, where people can get adequate sun exposure.^[32-34] It has been reported that more than one-third of human adults have low 25(OH)D levels.^[35] In addition, VD deficiency is often severe and significantly more seen in elderly people.^[36]

The present study aims to evaluate the potential relationship between VD deficiency and six given risk factors: age, sex, body mass index (BMI), renal function, history of cholecystectomy, and the most frequent drugs taken by the elderly.

METHODS

Study design

Data of all patients admitted to the acute geriatric unit between November 2015 and April 2016 were analyzed. There were 125 patients, 52 men and 73 women. Patients were divided into two subgroups according to their age:

old-old ($\geq 75-84$ years) and oldest-old patients (>84 years) [Figure 1].^[37] These patients were interviewed and asked about their current intake of VD supplements as well as any previous prescription of VD taken during the preceding 3 years. Since VD supplementation could affect the serum 25(OH)D level for 3 years,^[38] an inability to obtain a detailed medication history for the preceding 3 years was the sole exclusion criteria.

We studied the association between serum 25(OH)D level and six parameters: age, sex, BMI, renal function, cholecystectomy history, and the influence of the prescribed drugs, such as furosemide, hydrochlorothiazide, fludione, Coumadin, aspirin, clopidogrel, nebivolol, bisoprolol, irbesartan, amlodipine, atorvastatin, oxazepam, lorazepam, zopiclone, zolpidem, esomeprazole, tramadol, and modopar. To obtain the most accurate results possible, we excluded patients having VD supplementation when we studied the association between 25(OH)D status and these parameters.

Laboratory assessments

On the same day, serum concentrations of calcium, albumin, intact parathyroid hormone (PTH), creatinine, and 25(OH)D were measured.

25(OH)D levels were categorized as follows: (1) very severe VD deficiency: <12.5 nmol/L; (2) severe VD deficiency: 12.5–24 nmol/L; (3) moderate VD deficiency: 25–49 nmol/L; (4) minor VD deficiency: 50–74 nmol/L; and (5) normal VD level: 75–175 nmol/L.^[39-41]

Glomerular filtration rate (GFR) was estimated by the CKD-EPI (Chronic Kidney Disease – Epidemiology Collaboration) equation in ml/min/1.73m². GFR levels were classified as the following: (1) normal GFR: ≥ 90 ; (2) slightly decreased GFR: 60–89; (3) chronic renal failure (CRF) at stage 3A: GFR between 45 and 59; (4) CRF at stage 3B: GFR between 30 and 44; (5) CRF at stage 4: GFR between 15 and 29; and (6) CRF stage 5: GFR <15 ml/min/1.73 m².^[42,43]

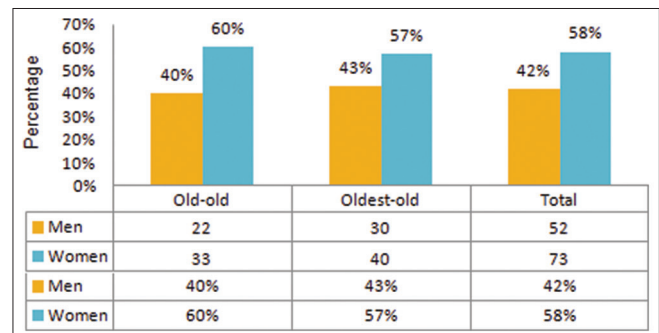


Figure 1: Age and sex distribution of the study sample of elderly patients. Patients were divided into two subgroups based on their age: old-old and oldest-old

The BMI was calculated as weight/height² in kg/m². Patient nutrition status was classified as follows: (1) very severe malnutrition: BMI <18; (2) malnutrition: BMI between 18 and 20.99; (3) normal body weight: BMI between 21 and 24.99; (4) preobesity: BMI between 25 and 29.99; (5) class I obesity: BMI between 30 and 34.99; (6) class II obesity: BMI between 35 and 39.99; and (7) class III obesity: BMI ≥40.^[44,45]

Statistical analysis

Data were analyzed using the Fisher’s exact test. *P* < 0.05 was considered statistically significant.

RESULTS

A high frequency of Vitamin D deficiency in the elderly

Most patients had 25(OH)D levels that were less than those currently recommended for optimal health. Furthermore, very severe and severe forms accounted for up to 43% [Figure 2].

Few elderly people receive Vitamin D supplementation

Our data showed that no VD supplement treatment was given to more than 75% of patients during the preceding 3 years [Figure 3a]. Patients’ age and gender had no association with this gap of VD prescription [Figure 3b].

Elderly men are more likely to suffer from very severe Vitamin D deficiency

Our data analysis showed that the prevalence of very severe VD deficiency in elderly men and elderly women was 44% and 26%, respectively. This difference was statistically significant [Figure 4].

There is no relationship between Vitamin D deficiency and age among the elderly

Our results showed that no significant difference in serum 25(OH)D level was observed between “old-old” and “oldest-old” subgroups [Figure 5], indicating that the age cannot be considered as a risk factor of VD deficiency in elderly people.

Vitamin D deficiency affects elderly people with normal renal function

GFR was evaluated in patients with very severe VD deficiency. We found that those patients had normal or mildly impaired renal function [Figure 6], indicating that elderly people can suffer from VD deficiency regardless of renal function status.

Obesity in elderly people does not worsen Vitamin D deficiency

Our data showed that no relationship was observed between the calculated BMI and the serum 25(OH)D level [Figure 7].

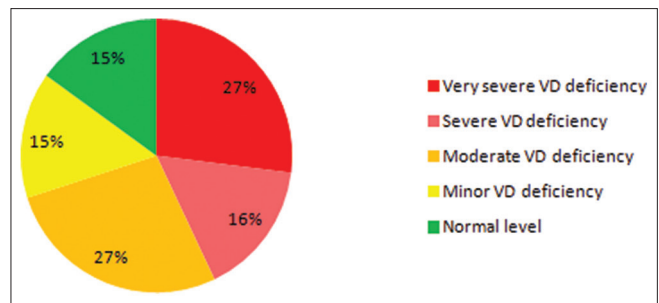


Figure 2: Vitamin D status in the study patient sample. More than a quarter of the patients were classified as “very severe Vitamin D deficiency” group. The Vitamin D recommended level was found only in 15% of the patients. No toxic levels were detected

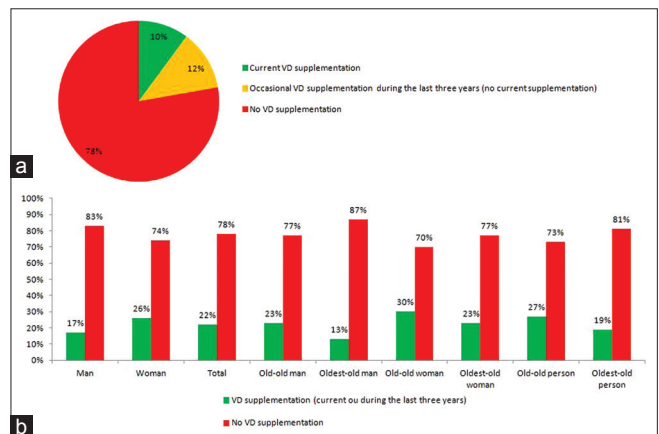


Figure 3: The rate of Vitamin D prescription. (a) The large majority of patients did not receive any Vitamin D supplementary treatment. (b) Vitamin D prescription in the different patient’s subgroups

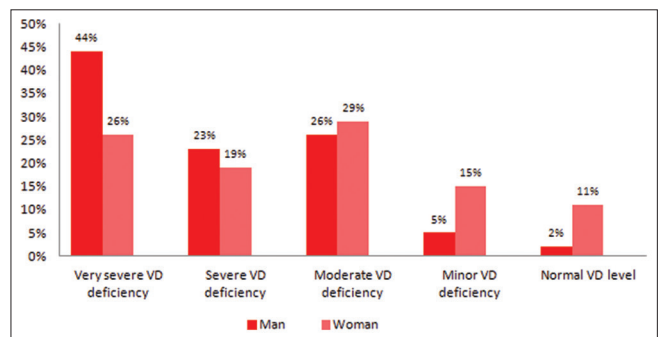


Figure 4: The sex effect on Vitamin D deficiency in elderly people. Elderly men are more affected by Vitamin D deficiency than women (*P* Fisher = 0.041: men vs. women in the “very severe Vitamin D deficiency” group)

P Fisher < 0.05 was 0.256 for the comparison between obese patients and those with a normal BMI.

Cholecystectomy has no effect on 25-hydroxyvitamin D level in the elderly

Our findings showed that cholecystectomy does not affect the VD deficiency prevalence in the elderly [Figure 8]. *P* Fisher = 0.38 for the comparison between patient with VD deficiency and those with normal 25(OH)D status.

P Fisher = 0.43 for the comparison between patient with very severe VD deficiency and those with normal 25(OH)D status.

Furosemide increases serum 25-hydroxyvitamin D levels

Furosemide is a loop diuretic commonly used in elderly patients (38% of our patients). Our data analysis showed that the furosemide therapy was significantly associated with normal serum 25(OH)D levels [Figure 9]. P Fisher = 0.037 for the comparison between patients with VD deficiency and those with normal 25(OH)D status. P Fisher = 0.024 for the comparison between patients with very severe VD deficiency and those with normal 25(OH)D status.

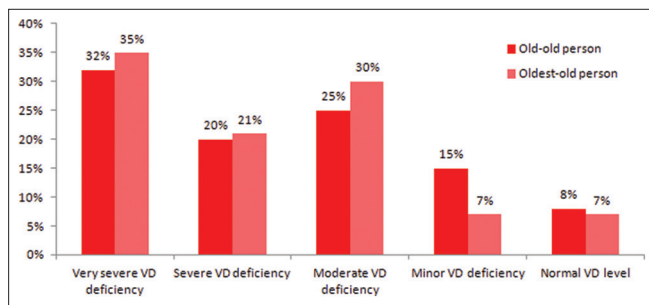


Figure 5: The age effect on Vitamin D deficiency in elderly people. No significant effect of patient age was observed on their Vitamin D status (P Fisher ≥ 0.3)

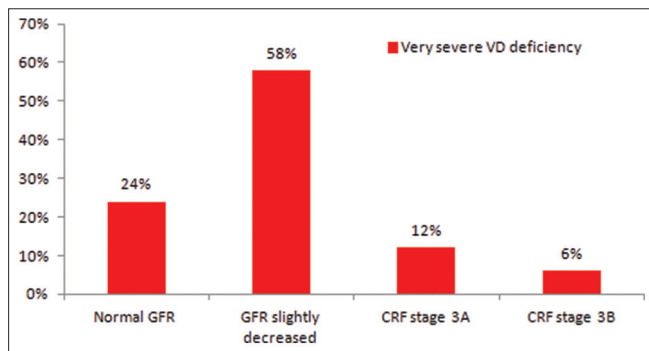


Figure 6: Renal function status in elderly people with very severe Vitamin D deficiency. 24% of patients had very severe Vitamin D deficiency despite of normal renal function

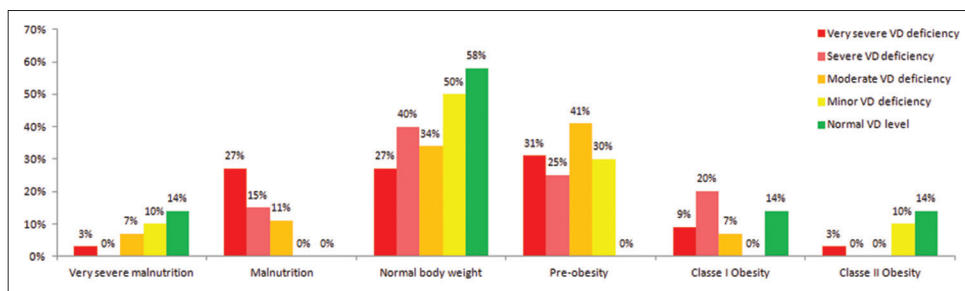


Figure 7: The effect of body mass index in elderly people on their Vitamin D deficiency. No significant difference in Vitamin D status was found (P Fisher ≥ 0.1)

Furosemide increases the risk of secondary hyperparathyroidism

Our results showed that furosemide administration was associated with a greater chance of developing secondary hyperparathyroidism (sHPT). This association was statistically significant (P Fisher = 0.0084) [Figure 10].

DISCUSSION

The prevalence of VD deficiency is still notably elevated. In the current study, only 15% of elderly people showed normal serum 25(OH)D level. Recent studies from France have also shown a small percentage of elderly people with normal VD status (6%–7.5%).^[46,47]

A large-scale study has investigated the VD deficiency prevalence in adults aged 18–74 years in France.^[39] This study demonstrated that very severe, severe, and moderate VD deficiencies were reported in 0%, 4.4%, and 36.7% of individuals, respectively. Furthermore, more than 50% of individuals had a serum 25(OH)D level >50 nmol/L. Nevertheless, the prevalence in the present study was 27%, 16%, 27%, and 30% for very severe, severe, moderate VD deficiency, and for those with serum 25(OH)D levels >50 nmol/L, respectively.

These outcomes demonstrate that VD deficiency is a public health problem, predominately in the elderly. Lack of physical activities and sun exposure are most likely the key reasons behind this relevant VD deficiency in elderly people.^[48] In addition, VD synthesis in the skin is reported to be widely diminished in the elderly.^[49]

An adequate VD and calcium intake should be achieved at any age, especially in childhood and in the elderly.^[50] Our data analysis showed that 78% of elderly people had not received any VD supplementation during the last 3 years. Furthermore, 90% of elderly patients are not taking any current VD supplements. A daily VD intake of 400 IU is recommended in France for individuals aged 65 years and

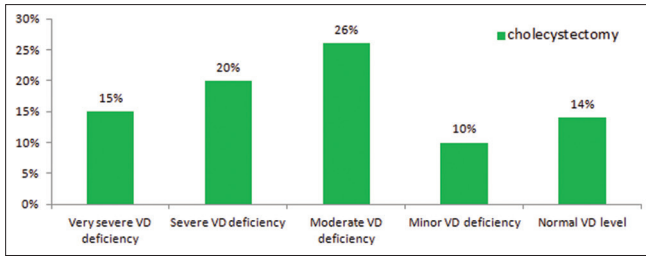


Figure 8: The association between Vitamin D status in elderly people and cholecystectomy history. Cholecystectomy has no significant effect on Vitamin D deficiency

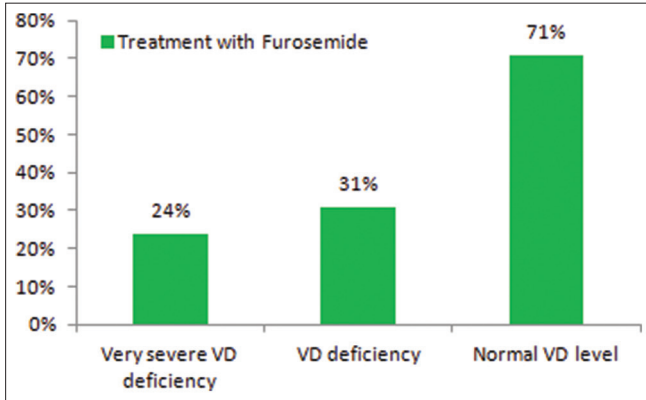


Figure 9: Furosemide treatment affects the Vitamin D status in elderly patients. Normal serum Vitamin D levels are more likely associated with the furosemide administration

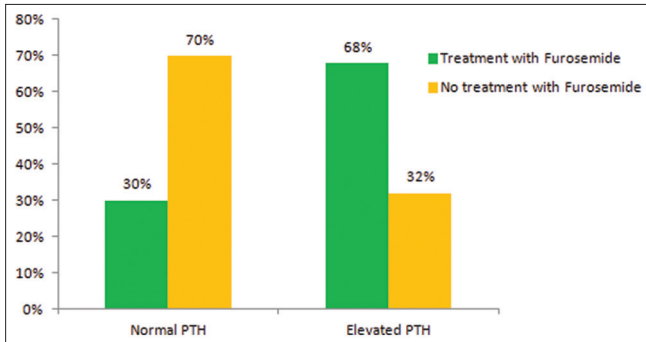


Figure 10: The relationship between furosemide treatment and parathyroid hormone status. A significant association between the increased level of parathyroid hormone and the furosemide treatment was observed (P Fisher = 0.0084)

over.^[51] However, many recent studies have recommended a daily dietary intake of VD ranging from 800 to 1000 IU.^[52-54] Unfortunately, these recommendations are poorly followed in clinical practice, even in high-risk individuals for VD deficiency.^[55] The daily average of VD intake in the elderly ranges from 100 to 200 IU in the developed countries, such as the UK, Ireland, Denmark, the Netherlands, France, Germany, Hong Kong, Japan, and Canada.^[36]

Our results showed that the very severe VD deficiency is seen more frequently in elderly men. This result seems to be

inconsistent with the findings of some previous studies.^[56-60] These studies have reported that the low 25(OH)D levels in the elderly were seen more commonly in women compared to men.

As recently reported by Cheng *et al.*,^[57] our data demonstrated that although VD deficiency is common in elderly people,^[61,62] the difference between old-old and oldest-old individuals is insignificant. Thus, all old people could be at a high risk of VD deficiency and they should receive VD supplement treatment regardless of their ages.

In the present study, no association between obesity and VD deficiency in the elderly was observed. This result seems to be consistent with a recent study from France.^[60] While Araghi *et al.*^[63] concluded that obesity in the elderly was associated with an increase in VD deficiency prevalence, Cheng *et al.*^[57] demonstrated that this relationship with obesity was seen only in elderly women.

The surgical history of cholecystectomy is frequently seen in elderly people. In the present study, 20% of the patients had undergone cholecystectomy. Given that bile salts are required for an efficient lipid and fat-soluble molecule absorption such as VD, cholecystectomy affects VD absorption.^[64,65] To the best of our knowledge, to date, no data are available in the literature on the effect of cholecystectomy on 25(OH)D level in the elderly. Our analysis result did not show any association between cholecystectomy and 25(OH)D status. This outcome could be due to the recovery of postcholecystectomy syndrome within several weeks.^[66]

Renal function alterations are associated with an increasing VD deficiency rate.^[67] Indeed, it is due to the decreased renal 1- α -hydroxylase activity in addition to diminished hepatic 25-hydroxylase function related to uremia.^[43,68,69] Our study showed that elderly people can suffer from very severe VD deficiency, even with normal renal function status.

PTH plays a key role in calcium metabolism in the body as it stimulates bone reabsorption, increases serum calcium and phosphorus levels, and promotes synthesis of 1,25(OH)₂D.^[70] The main regulator for PTH secretion is the calcium-sensitive receptor (CaSR).^[71] Activation of CaSR by calcium inhibits rapidly PTH synthesis. In addition, the parathyroid glands express high levels of VD receptors, which, when activated by binding to 1,25(OH)₂D, decreases PTH synthesis. In contrast, VD deficiency stimulates PTH synthesis.^[72] Furosemide is a loop diuretic that enhances urinary calcium excretion.^[73] Our study showed that furosemide treatment is associated with an increased prevalence rate of sHPT in the elderly. This effect is already observed in furosemide-treated patients

in the general population.^[74-77] Hyperparathyroidism is associated with progressive vascular calcification and increases cardiovascular morbidity and mortality.^[78-80]

sHPT is one of the methods used to determine the reference range for serum 25(OH)D concentration. Using this method, the lowest normal limit of serum 25(OH)D concentration is found to be 75 nmol/L.^[81] Surprisingly, we demonstrated in the present study that furosemide administration is associated with normal serum 25(OH)D levels. Thus, the current normal threshold of serum 25(OH)D concentration for furosemide-treated patients must be reconsidered.

Some pharmacological therapies for systolic heart failure are associated with reduced morbidity and mortality, such as beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and aldosterone antagonists.^[82] However, many recent studies highlighted the high mortality rates associated with furosemide use.^[83-85] It may be worthwhile, in the future studies, to investigate the plausible association between the furosemide-induced sHPT and the increased mortality. Therefore, our findings suggest that the increase of the minimal normal VD levels in serum up to an adequate proportional value associated with normal PTH concentration may lead to reduce the furosemide-related mortality.

CONCLUSION

VD has all the characters of a hormone.^[86] In the clinical practice, hypothyroidism, adrenal insufficiency, or other endocrine disorders get the full attention of physicians with good established treatment protocols; VD deficiency should be fully treated; and such a high rate of VD deficiency should not be accepted.

Like many other studies conducted in Europe, the present work showed that in such a rich region of the world, VD deficiency issues in the elderly cannot be adequately resolved by a simple change in food habits or even by food enrichment. Thus, pharmacological supplementation seems to be essential to prevent VD deficiency.

Our study indicates, for the first time, the great importance in determining the normal 25(OH)D threshold for furosemide-treated individuals.

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Conflicts of interest

There are no conflicts of interest.

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