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Andersen, Charlotte Uggerhøj; Strandhave, Charlotte; Thaarup, Maja; Poulsen, Maria Bitsch; Andersen, Stig; Olesen, Anne Estrup

Published in:
PharmaNutrition

DOI (link to publication from Publisher):
10.1016/j.phanu.2021.100274

Publication date:
2021

Document Version
Publisher's PDF, also known as Version of record

PharmaNutrition 17 (2021) 100274

Contents lists available at ScienceDirect

PharmaNutrition

journal homepage: www.elsevier.com/locate/phanu

Elderly patients with hip fracture and subnormal renal function have inadequate response to vitamin D supplementation

Charlotte Uggerhøj Andersen [a,b,c,*], Charlotte Strandhave [a,c,d], Maja Thaarup [a,e], Maria Bitsch Poulsen [a,e], Stig Andersen [c,f], Anne Estrup Olesen [a,c]

[a] Department of Clinical Pharmacology, Aalborg University Hospital, Aalborg, Denmark
[b] Department of Clinical Pharmacology, Aarhus University Hospital, Aarhus, Denmark
[c] Department of Clinical Medicine, Aalborg University, Aalborg, Denmark
[d] Department of Nephrology, Aalborg University Hospital, Aalborg, Denmark
[e] The Faculty of Medicine, Aalborg University, Aalborg, Denmark
[f] Department of Geriatric and Internal Medicine, Aalborg University Hospital, Aalborg, Denmark

ARTICLE INFO

Keywords:
Osteoporosis
Hyperparathyroidism
Nutritional supplements
Calcium
Diuretics

ABSTRACT

Introduction: All Danish citizens aged >70 years are recommended to take vitamin D supplements. We hypothesized that renal insufficiency may impair the activation and effect of vitamin D supplements. We aimed to investigate the association between use of vitamin D supplements, and levels of 25-hydroxy-vitamin D and parathyroid hormone (PTH) in elderly patients according to estimated glomerular filtration rate (eGFR).
Methods: The study was a sub-analysis of 164 patients with 25-hydroxy-vitamin D levels measured in a cross-sectional study of 200 consecutive patients aged ≥65 years admitted to hospital with hip fracture.
Results: Vitamin D supplement-users (n = 68) had significantly higher 25-hydroxy-vitamin D levels regardless of eGFR ≤ or>60 ml/min. In patients with eGFR>60 ml/min (n = 103), median PTH levels were significantly lower in vitamin D supplement-users compared to non-users (4.8 [4.2–6.7] vs 6.25 [4.9–8.3] pmol/l, P = 0.039), while there was no difference in patients with eGFR≤60 ml/min (9.5 [5.4–16.7] vs 9.8 [5.9–16.9] pmol/l, P = 0.66 (n = 61)).
Conclusions: Use of vitamin D supplements was associated with increased levels of 25-hydroxy-vitamin D, but only associated with decreased levels of PTH in patients with eGFR>60 ml/min. Thus, renal function may be essential to gain effect of vitamin D supplements, and 25-hydroxy-vitamin D levels may not reflect active Vitamin D status in elderly vitamin D supplement-users with hip fracture and decreased renal function. In addition to current guidelines for prescription of vitamin D supplements, it may be considered to monitor PTH or active vitamin D in elderly patients with eGFR<60 ml/min and adjust dose accordingly.

1. Introduction

Vitamin D (VD) is important for calcium homeostasis and plays a pivotal role for skeletal health. VD deficiency is common in patients with hip fractures [1–7], and these patients pose a high economic burden on health and social care systems due to hospitalization and rehabilitation costs, which will increase with the aging population [8,9].

The main circulating and biologically inert 25-hydroxy VD is converted to the active form 1,25-dihydroxy VD in the kidney, and although the enzyme adding this hydroxyl group is expressed in other tissues [10], renal function is considered important to gain the beneficial effect of both endogenous, dietary and supplemented VD [11]. The biologically active form of VD (1,25-$(OH)_2$ VD) is crucial for optimal bone formation as it influences the intestinal absorption and renal reabsorption of calcium and phosphate [12,13]. Insufficient levels of active VD can cause secondary hyperparathyroidism in which PTH-levels increase in response to decreased calcium levels, and helps maintain the extracellular calcium and phosphate levels, partly, through osteoclast activation [14]. Thus, an increased PTH level may be a marker of insufficient levels of active VD, and it is often used as a surrogate marker of the effect of treatment with VD supplements (VDS) [15]. Furthermore, persistent secondary hyperparathyroidism over a longer period

* Corresponding author at: Department of Clinical Pharmacology, Aalborg University Hospital, Mølleparkvej 8, 9000, Aalborg, Denmark.
E-mail address: c.uggerhoej@rn.dk (C.U. Andersen).

https://doi.org/10.1016/j.phanu.2021.100274
Received 6 May 2021; Received in revised form 29 June 2021; Accepted 29 June 2021
Available online 30 July 2021

deter bone structure and increase the risk of osteoporosis [14,16–18].

Clinical practice guidelines recommend VDS at suggested daily intake and tolerable upper limit levels, depending on age and clinical circumstances [19]. Some studies have shown that VDS may reduce the risk of fractures [20], while meta-analyses have reported inconsistent results regarding the association between calcium, VDS and fracture risk [21–26]. Thus, the current evidence is insufficient to assess the benefits and harms of VD and calcium supplementation for prevention of fractures [27].

The decrease in renal function accompanied by raised fracture risk with advancing age led us to hypothesize that insufficient renal activation of VD decreases the effect of VDS. Accordingly, the aim of this explorative study was to evaluate the association between the use of VDS, plasma levels of 25-hydroxy VD and PTH in elderly hip fracture patients, and to elucidate if decreased renal function may be an effect modifier to this association.

2. Methods

2.1. Study design and population

The present study is an extension of a previous study by Andersen et al. on medicine use in hip fracture patients [28]. In brief, this was a retrospective cross-sectional study including 200 consecutive patients aged above 65 years admitted to a Danish University Hospital during a period of 24 weeks in 2017. Only patients in whom levels of 25-hydroxy VD were measured during the admission were included in the present study.

2.2. Clinical and laboratory data

The following data was extracted from all patient records: 1) characteristics including age, gender, BMI, and previous fractures, 2) laboratory data including plasma levels of 25-hydroxy VD, PTH, P-creatinine, and estimated glomerular filtration rate (eGFR), and 3) use of VDS (≥20 μg (400 IU) daily), furosemide, oral glucocorticoids, and medication for osteoporosis (bisphosphonates or denusomab), at the time of admission.

Levels of 25-hydroxy VD, creatinine, and eGFR are reported from the routine analysis conducted by the standard laboratory methods used at the department of clinical biochemistry at the hospital. An eGFR above 90 ml/min are given the value 91 ml/min in the report but may be higher.

2.3. Data handling and statistical analysis

The study data was collected and managed using the Research Electronic Data Capture (REDCap) (Vanderbilt, USA) hosted at Aalborg University Hospital. REDCap is a secure, web-based application designed to support data capture for research studies [29]. Data were exported for statistical analysis in STATA (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, TX: StataCorp LLC). Box and whisker plots were constructed using Microsoft excel.

Normal distribution of data was checked by Shapiro-Wilks test. Parametric data were expressed as mean ± standard deviation (SD), and non-parametric data as medians [25th percentile - 75th percentile]. Patients were divided according to whether they used a VDS of ≥20 μg (400 IU) daily, and for evaluation of the impact of renal function, they were divided in two groups with an eGFR≤60 ml/min, and an eGFR>60 ml/min, respectively. Differences between the two groups were analyzed by student's *t*-test (parametric data) or Wilcoxon's rank sum test (non-parametric data). $\chi 2$ test was used for comparison of binary outcomes. Differences between multiple groups were analyzed by Kruskal-Wallis test. Analyses were performed without imputation of missing data due to few missings. The numbers of included patients are provided in tables or figures if data were not available for all patients. A p value below 0.05 was considered statistically significant.

2.4. Ethics

In accordance with Danish legislation (Act on Research Ethics Review of Health Research Projects § 14 stk. 2 dated 15/09/2017 and the Danish Health Act § 46 stk. 2 dated 02/11/2018), approval was obtained from the Danish Patient Safety Authority. The study was registered at the Danish Data Protection Agency, and Data were handled in accordance with the Danish Personal Data Protection Act.

3. Results

Levels of 25-hydroxy VD were measured in 164 patients, of whom 68 (41.5 %) used VDS at the time of admission. In 47 patients (28.7 %) VDS was combined with calcium supplement. Patients using VDS were older, more likely to have previous fractures, and to use medication for osteoporosis. Furthermore, they had higher median levels of 25-hydroxy VD (Table 1). There were no significant differences in sex, PTH, P-creatinine levels or eGFR (Table 1).

Sixty-one (37.2 %) of the 164 patients had an eGFR≤60 ml/min. This group had a higher median age, a higher BMI, and higher median levels of PTH compared to those with eGFR>60 ml/min. Furthermore, they were markedly more likely to use furosemide (Table 2). Serum 25-hydroxy VD levels were significantly higher in those who used VDS among both patients with eGFR≤ 60 ml/min and >60 ml/min (Fig. 1a). In patients with eGFR>60 ml/min, median levels of PTH were significantly lower in VDS-users compared to non-users (4.8 [4.2–6.7] vs 6.25 [4.9–8.3] pmol/l, P = 0.039). However, median PTH levels in patients with eGFR≤60 ml/min did not differ between VDS-users and non-users (9.5 [5.4–16.7] vs 9.8 [5.9–16.9] pmol/l, P = 0.66) (Fig. 1b). Furthermore, patients with a daily intake of VDS counted more furosemide-users and fewer men compared to VDS non-users in the group of patients with eGRF≤60 ml/min (Table 2).

No seasonal variation in VD levels was observed when dividing the patients into groups based on two-month periods for measurements of the VD level (p = 0.92). Oral glucocorticoids were used by five patients (3 %) of which the majority used VDS and had eGFR>60 ml/min.

4. Discussion

The main finding of the present study was that renal function even at the level of 60 ml/min in eGFR modified the effect of VDS in hip fracture patients. Levels of PTH in serum were lower in users compared to non-users of VDS when eGFR was above 60 ml/min. Interestingly, this association was absent in patients with an eGFR below or equal to 60 ml/min, even when levels of 25-hydroxy VD were significantly higher in those who used VDS.

In general, use of VDS was associated with previous fractures and use of medication for osteoporosis, which is in line with clinical recommendations on prescriptions to ensure adequate VD and calcium. Furthermore, the majority of patients taking oral glucocorticoids used VDS. However, the prevalence of oral corticoid-users in our population was very low, and therefore, we will not elaborate further on this. Interestingly, use of VDS was associated with furosemide intake and female sex in those with eGFR≤60 ml/min, but not in the rest of the patients. Thus, our hypothesis that decreased renal function contributes to the absent association between use of VD supplement and PTH levels cannot be excluded. However, use of furosemide and female sex may also play a role. Use of furosemide was an important risk factor for secondary hyperparathyroidism in nursing home residents in a previous study [30], and use of loop diuretics was associated with increased PTH levels in patients with chronic kidney failure, probably due to increased excretion of calcium in urine [31]. However, it is unclear why loop diuretics should per se decrease the effect of VDS on PTH levels, although it could be speculated that the supplemented VD dose is insufficient to

Table 1
Characteristics of the study population.

		Total population N = 164	VDS N = 68	No VDS N = 96	P-value VDS vs no VDS
Age	Years	82 [76.5–88]	83 [77–91]	81 [75–86]	0.01
Bmi	Kg/m^2	24 ± 4.4 (N = 142)	23.7 ± 4.5 (N = 59)	24.4 ± 4.2 (N = 83)	0.3
Male sex	N (%)	55 (33.5)	18 (26.5)	37 (38.5)	0.11
Previous fractures	N (%)	27 (16.5)	19 (27.9)	8 (8.3)	0.009
Use of medication for Osteoporosis	N (%)	28 (17.1)	24 (35.3)	4 (4.2)	<0.001
Use of furosemide	N (%)	47 (36)	25 (36.7)	22 (22.9)	0.053
Use of systemic glucocorticoids	N (%)	5 (3.0)	4 (5.8)	1 (1.0)	0.07
25-hydroxy Vitamin D	nmol/L	68 [37–92.5]	85 [64.5–107.5]	46 [25–79]	<0.001
PTH	pmol/L	6.6 [4.7–9.6] (N = 150)	6.1 [4.3–9.4] (N = 61)	6.7[5–9.7] (N = 89)	0.12
P-Creatinine	μmol/L	77 [60.5–104]	78.5 [56.5–98]	75 [61–108]	0.78
eGFR*	ml/min	71 [48–84]	67.5 [48.5–82]	71.5 [47.5–85]	0.53

VDS = vitamin D supplement, N = number, Bmi = Body mass index, eGFR = estimated glomerular filtration rate. Numerical data are expressed as median [25th percentile, 75th percentile], or mean ± standard deviation.

Table 2
Characteristics according to eGFR and use of VD supplement.

	eGFR≤60	eGFR>60		eGFR≤60			eGFR>60		
	N = 61	N = 103	P-value eGFR≤vs>60	VDS N = 28	No VDS N = 33	P-value + VD vs −VD	VDS N = 40	No VDS N = 63	P-value + VD vs −VD
Age	87 [79–91]	81 [73–85]	<0.001	90 [80–93]	86 [79–88]	0.09	82 [75.5–87.5]	79 [73–84]	0.09
Bmi	25.2 ± 3.9 (N = 53)	23.5 ± 5.6 (N = 89)	0.035	24.3 ± 4.1 (N = 24)	25.8 ± 3.6 (N = 29)	0.17	23.3 ± 4.3 (N = 35)	23.7 ± 4.9 (N = 54)	0.7
Male sex	24 (39.3)	31 (30.1)	0.22	6 (21.4)	18 (54.5)	0.008	12 (30.2)	19 (30.2)	0.9
Previous fractures	10 (16.4)	17 (16.5)	0.9	7 (25)	3 (9.1)	0.09	12 (30)	5 (7.9)	0.003
Use of osteoporosis medication	12 (19.7)	16 (15.5)	0.49	9 (32.1)	3 (9.1)	0.02	15 (37.5)	1(1.6)	<0.001
Use of furosemide	32 (52.5)	15 (14.6)	<0.001	19 (67.8)	13 (39.4)	0.027	6 (15.0)	9 (14.3)	0.9
Creatinine (μmol/L)	116 [96–147]	65 [54–75]	<0.001	103 [91.5–138]	129 [108–147]	0.09	61 [50–73.5]	67 [56–75]	0.25
eGFR (ml/min)*	42 [35–49]	82 [72–88]	<0.001	44 [35–51.5]	42 [35–48]	0.52	81.5 [74–87]	82 [72–89]	0.9

Abbreviations: VDS = vitamin D supplement, eGFR = estimated glomerular filtration rate, Bmi = Body mass index.
* eGFR values higher than 90 ml/min are given the value 91 ml/min, but may be higher.

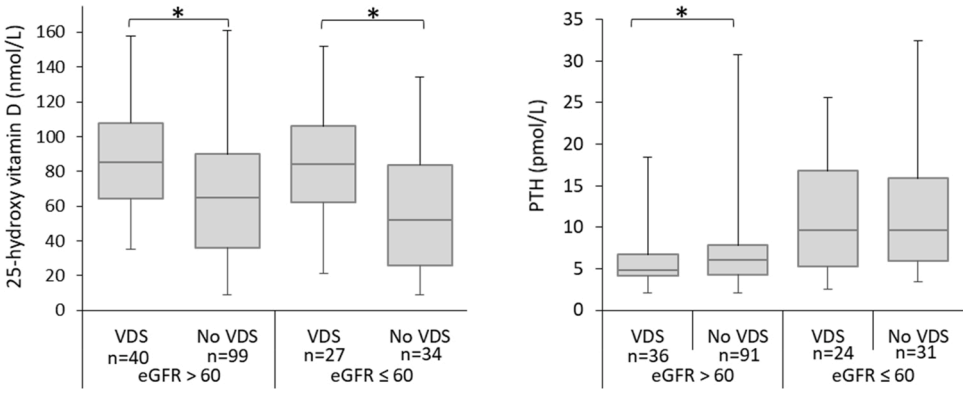

Fig. 1. VD and PTH levels in VDS users and non-users according to eGFR.
Box and whiskers representing median value, interquartile range, minimum, and maximum value of 25-hydroxy VD (a) and PTH levels (b). One outlier value of PTH in the no VDS group with eGFR≤60 was excluded. * = p-value <0.05. Abbreviations: VDS = Vitamin D supplement, eGFR = estimated glomerular filtration rate (ml/min), PTH = parathyroid hormone.

correct the increased excretion of calcium. On the other hand, the association between use of VDS, female sex, and use of furosemide could be the result of covariation of these factors with the overall risk of osteoporosis or living in a nursery home, and a resulting higher probability for being prescribed VDS. Furosemide was widely used in our study population, and in the previous report on medication-related falls based on this population, furosemide was suspected to contribute to the fall preceding a hip fracture in 7.5 % due to its adverse effects including dehydration and orthostatic hypotension [28]. The apparent association to increased PTH levels and reduced effect of VDS further encourages restricted use of furosemide in elderly people with raised risk of hip fracture.

The absence of the expected association between the use of VDS and PTH levels in patients with eGFR ≤60 ml/min in our study suggests that the effect of VDS is hampered in these patients. We obtained information on VD supplement use from the patient record in which the attending physician is legally obliged to secure information on used medication and nutritional supplements prior to the admission. Thus, the data regarding medicine use is reliable and confirmed by the higher levels of 25-hydroxy VD in those registered as VD supplement users. A meta-analysis of randomized controlled trials [20] reported that in general, VDS did not significantly reduce the risk of hip fractures in elderly people. However, in a sub analysis, there was a statistically significant reduction of the risk among those treated with the highest VD doses ranging from 792 to 2000 IU corresponding to approximately 20–50 μg pr. day [19,20]. This may suggest that the cut-off level for VD dose used

in our study population should be effective. However, eGFR levels were not considered in the meta-analysis. In one of the studies included, two years treatment with VDS decreased intact PTH levels compared to placebo [32], which may seem to contrast to the observations in our study. The study was considerably larger than the present and was a randomized controlled study. However, elderly with P-creatinine levels >150 μmol were excluded, and sub-analysis in participants according to renal function was not performed [32], suggesting that a differentiated effect between patients with and without decreased renal function is not precluded. In a study from 2017, VDS with two doses of 300.000 IU (7.500 μg) given eight weeks apart to patients with chronic kidney disease stage 1–4 resulted in both increased levels of the active 1, 25-$(OH)_2$-VD, and decreased levels of PTH after 16 weeks [33]. The dose of VDS used was markedly higher than those used by patients in our study, and the effect on PTH may be explained by extra-renal activation of VD. Furthermore, the included patients were considerably younger than the typical hip fracture patient. In our study, measurements of 25-hydroxy VD levels were available as it is analyzed routinely in our hospital in line with guidelines [19]. However, measurement of the biologically active 1,25-$(OH)_2$-VD would have allowed us to approach whether decreased activation of VDS could explain why the higher 25-hydroxy VD levels in VDS-users were not reflected in decreased PTH levels in patients with eGFR ≤60 ml/min. Thus, further research should elucidate the effect of VDS on 1,25-$(OH)_2$-VD and PTH levels in hip fracture patients with slightly decreased renal function.

4.1. Study limitations

Our study population consisted of a selected group of elderly patients admitted to hospital with hip fracture. The majority were older than 70 years of age, and we expected a higher prevalence of VDS-users than the observed 41.5 % in order to comply with clinical practice guidelines in general and with the recommendations from the Danish health authorities. We cannot exclude that this apparently low adherence to recommendations may be due to an association between failure to use the VDS, a poorer bone health, and a consequently higher propensity for hip fracture, and that this potential selection bias may affect the results.

Moreover, multi morbidity and polypharmacy was frequent in our population, but we only considered medication such as furosemide, which have previously been linked to increased levels of PTH. Levels of calcium were not taken into consideration, due to lack of availability in most patients. Furthermore, information on duration of VDS intake before admission by the individual patient was not available.

A prospective study design with a larger sample size could support complete data and allow the use of multiple regression analysis to evaluate the relationship between VD level, PTH level and renal function to determine if age, gender, BMI, and other medications would influence the association between renal function, VD and PTH.

5. Conclusions

Use of VDS was associated with increased 25-hydroxy VD levels in all patients, but lower PTH levels were only seen in patients with eGFR above 60 ml/min. This interesting finding indicates that normal renal function may be essential for the beneficial effect of VDS. Thus, higher doses of VDS or activated VD may be necessary to prevent secondary hyperparathyroidism and reduce hip fracture risk in elderly patients with slightly decreased renal function. We recommend following current guidelines for the prescription of VDS to elderly. In addition, it should be considered to monitor PTH and active 1,25-(OH)2-VD in patients with eGFR <60 ml/min and adjust the dose of VD accordingly.

Financial disclosure statement

No funding was received.

Transparency document

The Transparency document associated with this article can be found in the online version.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgment

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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