



Original Article

Elderly with proximal hip fracture present significantly lower levels of 25-hydroxyvitamin D[☆]



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ARTICLE INFO

Article history:

Received 14 January 2016

Accepted 15 February 2016

Available online 31 August 2016

Keywords:

Vitamin D deficiency

Hip fractures

Osteoporotic fractures

ABSTRACT

Objective: To compare serum 25-hydroxyvitamin D (25[OH]D) levels, a serum marker of vitamin D3, between patients with and without proximal hip fracture.

Methods: This was a case-control study in which serum samples of 25(OH)D were obtained from 110 proximal hip fracture inpatients and 231 control patients without fractures, all over 60 years of age. Levels of 25(OH)D lower than or equal to 20 ng/mL were considered deficient; from 21 ng/mL to 29 ng/mL, insufficient; and above 30 ng/mL, sufficient. Sex, age, and ethnicity were considered for association with the study groups and 25(OH)D levels.

Results: Patients with proximal hip fracture had significantly lower serum 25(OH)D levels (21.07 ng/mL) than controls (28.59 ng/mL; $p=0.000$). Among patients with proximal hip fracture, 54.5% had deficient 25(OH)D levels, 27.2% had insufficient levels, and only 18.2% had sufficient levels. In the control group, 30.3% of patients had deficient 25(OH)D levels, 30.7% had insufficient levels, and 38.9% had sufficient levels. Female patients had decreased serum 25(OH)D levels both in the fracture group and in the control group (19.50 ng/mL vs. 26.94 ng/mL; $p=0.000$) when compared with male patients with and without fracture (25.67 ng/mL vs. 33.74 ng/mL; $p=0.017$). Regarding age, there was a significant association between 25(OH)D levels and risk of fracture only for the age groups 71–75 years and above 80 years.

Conclusion: Patients with proximal hip fracture had significantly decreased serum 25(OH)D levels when compared with the control group. Female patients had significantly lower serum 25(OH)D levels in both groups.

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[☆] Study conducted at the Universidade Luterana do Brasil (Ulbra), Hospital Universitário, Departamento de Ortopedia e Traumatologia, Canoas, RS, Brazil.

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<http://dx.doi.org/10.1016/j.rboe.2016.08.013>

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Idosos com fratura da extremidade proximal do fêmur apresentam níveis significativamente menores de 25-hidroxivitamina D

R E S U M O

Palavras-chave:

Deficiência de vitamina D
Fraturas do quadril
Fraturas por osteoporose

Objetivo: Comparar os níveis séricos de 25-hidroxivitamina D [25(OH)D], marcador sérico da vitamina D3, entre pacientes com e sem fratura da extremidade proximal do fêmur (FEPF). **Métodos:** Estudo caso-controle em que foram obtidas amostras séricas de 25(OH)D de 110 pacientes com FEPF internados e de 231 pacientes de grupo controle que não apresentaram fraturas, todos acima de 60 anos. Níveis de 25(OH)D menores ou iguais a 20 ng/mL foram considerados deficitários; entre 21 ng/mL e 29 ng/mL, insuficientes; e acima de 30 ng/mL, suficientes. Foram consideradas as variáveis sexo, idade e etnia para associação com os grupos em estudo e os níveis de 25(OH)D.

Resultados: Pacientes com FEPF apresentaram níveis séricos de 25(OH)D significativamente inferiores (21,07 ng/mL) comparados com os do grupo controle (28,59 ng/mL; $p = 0,000$). Entre os pacientes com FEPF, 54,5% apresentaram níveis de 25(OH)D deficitários, 27,2% insuficientes e apenas 18,2% suficientes. Já no grupo controle, 30,3% dos pacientes apresentaram níveis deficitários, 30,7% insuficientes e 38,9% suficientes. Pacientes do sexo feminino apresentaram níveis séricos de 25(OH)D reduzidos tanto no grupo com fratura quanto no grupo controle (19,50 vs. 26,94 ng/mL; $p = 0,000$) comparados com os do sexo masculino com e sem fratura (25,67 vs. 33,74 ng/mL; $p = 0,017$). Quanto à idade, houve associação significativa entre os níveis de 25(OH)D e risco de fratura apenas para as faixas 71-75 anos e acima de 80.

Conclusão: Pacientes com FEPF apresentaram níveis séricos de 25(OH)D significativamente reduzidos em comparação com os do grupo controle. Pacientes do sexo feminino apresentaram níveis séricos de 25(OH)D significativamente menores em ambos os grupos.

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Introduction

Proximal femoral fracture (PFF) has a high incidence in patients older than 65 years and usually results from low-energy trauma. Despite the resources of modern medicine, there is a high mortality rate, around 25–30% yearly.¹⁻³ Mortality is mainly due to factors such as advanced age, comorbidities, previous cognitive impairment, and delay in the procedure.^{1,2} PFF also represents a major cost to public health, mainly due to prolonged hospitalization and related surgical procedures.^{3,4}

Vitamin D plays an important role in calcium metabolism, and consequently in bone mineralization and the osteoporotic picture. Its deficiency is therefore an important risk factor for PFF in the elderly.^{1,5,6} The best serum marker of this vitamin is 25-hydroxyvitamin D (25(OH)D), whose metabolic product is vitamin D3; values equal to or above 30 ng/mL are considered sufficient.⁷ The use of vitamin D3 has been recommended to prevent fractures in elderly patients with osteoporosis. However, it is not always routinely used in public healthcare.⁸⁻¹⁰

This study aimed to compare serum 25(OH)D levels among elderly patients with and without PFF, and to analyze the association of variables such as gender, age, and ethnicity with this condition.

Material and methods

This was a case-control study conducted in the Department of Orthopedics and Traumatology of this institution

between January 2013 and May 2015. The study was approved by the Ethics Committee of the institution under CAAE No. 33760914.8.0000.5349.

The fracture group comprised patients over 60 years with PFF. The study included patients with femoral neck, subtrochanteric, and transtrochanteric fractures who had experienced a low-energy fall. The control group included age-matched individuals without PFF history, recruited among the patients attended to at the orthopedics clinic and other medical specialties at this hospital, as well as inpatients admitted for non-orthopedic/traumatological reasons. The exclusion criteria comprised patients outside the age range; with fractures with known history of high energy; with missing data on medical records, such as ethnicity and sex; or with unknown serum levels or without results provided by the laboratory.

Serum 25(OH)D samples were collected for all patients. In the fracture group, blood samples were collected immediately after the patient's admission, before the final surgical procedure. In the control group, samples were collected after outpatient care. Serum levels were measured in a standard laboratory for all samples, measured as nanograms per milliliter (ng/mL).

The results of the blood collection of 25(OH)D were divided in accordance with the Horlick classification, where values below 20 ng/mL are considered deficient; between 21 and 29 ng/mL, insufficient; and above 30 ng/mL, normal.⁷ The variables gender, age, and ethnicity were considered for purposes of association with the study groups and levels of 25(OH)D.

In order to reject the null hypothesis that serum 25(OH)D would be equal in the case and control groups, the minimum

Table 1 – Sample characterization.

Variable	Group						p
	Control (n = 231)		Fracture (n = 110)		Total (n = 341)		
	n	%	n	%	n	%	
Ethnicity							
White	218	94.4	106	96.4	324	95.0	0.839 ^a
Black	9	3.9	3	2.7	12	3.5	
Mixed	4	1.7	1	0.9	5	1.5	
Sex							
Female	175	75.8	82	74.5	257	75.4	0.808 ^b
Male	56	24.2	28	25.5	84	24.6	
Age (years)							
60–65	24	10.4	12	10.9	36	10.6	0.850 ^b
66–70	16	6.9	8	7.3	24	7.0	
71–75	50	21.6	21	19.1	71	20.8	
76–80	51	22.1	20	18.2	71	20.8	
>80	90	39.0	49	44.5	139	40.8	

Source: Authors

^a Chi-squared test.^b Fisher's exact test.

sample size calculated to obtain statistically significant results was 60 patients with PFF (fracture group) and 120 patients without PFF (control group).

Statistical analysis

The statistical program used was SPSS, version 13.0. Results were considered significant at a level of 5% ($p \leq 0.05$). Data were expressed as mean and standard deviation or percentage (%). The statistical difference between the fracture and control groups and their respective variables was calculated with the chi-squared and Fisher's exact tests. The Kolmogorov-Smirnov test of normality indicated that the study variables did not present normal distribution; therefore, a nonparametric test was used in the analysis. The Mann-Whitney test was used to compare the mean serum levels of 25(OH)D between groups, and these values were stratified by age and gender. For the ethnicity variable, it was not possible to perform statistical tests due to the insufficient number of cases for the mixed and black ethnicities.

Results

The present sample comprised 341 patients. The fracture group included 110 patients, of whom 82 (74.5%) were female, and the control group consisted of 231 patients, of whom 175 (75.8%) were female. Mean age of the fracture patients was 78.76 ± 9.52 years, and mean age of the controls was 77.31 ± 7.85 years. There was no difference between groups regarding sex or age ($p > 0.05$). Sample characteristics are described in [Table 1](#).

The serum levels of 25(OH)D in the control group (28.59 ± 12.31 ng/mL) were significantly higher than in the fracture group (21.07 ± 10.28 ng/mL) ($p = 0.000$). In the fracture group, considering the Horlick classification, 54.5% ($n = 60$)

patients had deficient serum 25(OH)D levels, and only 18.2% ($n = 20$) had sufficient values. Among the controls, 38.9% ($n = 90$) were considered to have sufficient serum levels; 30.3% had deficient serum levels ($n = 70$) ([Table 2](#)).

There were no significant differences between the groups regarding the serum levels of 25(OH)D for the age ranges of 60–65 years ($p = 0.327$), 66–70 ($p = 0.417$), and 76–80 ($p = 0.095$). However, significant differences were observed in the age groups 71–75 years ($p = 0.003$) and over 80 ($p = 0.003$) ([Table 3](#)).

For the ethnicity variable, statistical analysis was not possible due to insufficient number of cases for the mixed and black ethnicities. Descriptive data for this variable are shown in [Table 4](#).

Regarding gender, a significant difference was observed in the levels of 25(OH)D between the groups. Lower serum 25(OH)D levels were observed in female patients, with a mean of 19.50 ± 10.01 ng/mL in the fracture group and 26.94 ± 11.23 ng/mL in the control group ($p = 0.000$). Among males, the mean was significantly higher in the control group (33.74 ± 14.08 ng/mL) when compared with the fracture group (25.67 ± 9.85 ng/mL, $p = 0.017$).

Table 2 – Serum levels of 25(OH)D in the fracture and control groups according to the Horlick classification.

25(OH)D	Control		Fracture		Total	
	n	%	n	%	n	%
Deficient	70	30.3	60	54.5	130	38.1
Insufficient	71	30.7	30	27.2	101	29.6
Sufficient	90	38.9	20	18.2	110	32.2
Total	231	100.0	110	100.0	341	100.0

Source: Authors

25 (OH) D, 25-hydroxyvitamin D.

Table 3 – Comparison of serum 25(OH)D between the fracture and control groups according to age group.

Age	Group	n	Mean	SD	p ^a
60–65 years	Control	24	31.5	11.52	0.327
	Fracture	12	24.1	14.38	
66–70 years	Control	16	32.22	10.58	0.417
	Fracture	8	29.19	11.79	
71–75 years	Control	50	28.43	11.37	0.3
	Fracture	21	20.50	8.33	
76–80 years	Control	51	30.82	9.96	0.95
	Fracture	20	25.83	9.61	
>80 years	Control	90	26.11	14.8	0.3
	Fracture	49	17.34	8.37	

Source: Authors

SD, standard deviation.

^a p=0.01.**Table 4 – Comparison of serum levels of 25(OH)D between the fracture and control groups according to ethnicity.**

Ethnicity	Control			Fracture		
	n	Mean	SD	n	Mean	SD
White	218	28.73	12.30	106	20.76	10.10
Mixed	9	23.38	10.77	3	29.59	16.32
Black	4	32.83	16.24	1	28.50	0.0

Source: Authors

SD, standard deviation.

Discussion

This study showed that patients with PFF had significantly lower serum 25(OH)D levels than the control group. Values considered insufficient in the Horlick classification were observed in both the control group (28.59 ng/mL) and in the fracture group (21.07 ng/mL). Considering this classification, half of patients with PFF had deficient levels of this vitamin. Low levels of 25(OH)D were also found in the control sample, with 30.7% of patients with insufficient levels and 30.3% deficient.

In a meta-analysis that included 15 case-control studies among patients with and without PFF, of the 17 patients analyzed, the serum levels of 25(OH)D in patients with fracture were significantly lower than in the control group.¹¹ Ramason et al.¹² conducted a study with 485 elderly with PFF and also found low levels of 25(OH)D in these patients, with a mean value of 19.1 ng/mL, 57.5% deficient, 34.5% insufficient, and only 8% had sufficient levels. Browne et al.,¹³ using a different serum measuring unit (nmol/L) in a study in Ireland with 156 elderly patients with PFF, found that over 67% of their sample had insufficient or deficient 25(OH)D serum levels. Gumiero et al.,¹⁴ in a Brazilian study on gait in patients with PFF, also observed low levels of 25(OH)D, with a mean value of 27.8 ng/mL; 33.7% of the sample had deficient values, which differs from the findings of the present study.^{7,14} Reduced serum levels of 25(OH)D were significantly related to PFF both in the present study and in previous studies;

however, specific differences in serum levels of this vitamin are recognized by various authors, due to its relation to sun exposure and the genetic characteristics of the local population.¹¹⁻¹³

Considering patients without PFF, Saraiva et al.¹⁵ also found the presence of hypovitaminosis in a study in an elderly population, having subdivided the sample into two groups. In the first group, consisting of hospitalized patients, 80% had 25(OH)D deficiency or insufficiency. In the second group, consisting of outpatients, lower values – albeit still significant – were observed: around 55% insufficiency or deficiency in serum levels, which are similar to those found in the control group of the present study.

Females had significantly lower levels of 25(OH)D in both groups of the present study, demonstrating the predominance of this hypovitaminosis in women, a feature recognized by many authors. In a review study, Patton et al. reported that 25(OH)D levels were comparatively lower in women, regardless of the cut-off criteria used.^{6,13-18} Labronici et al.,¹⁸ when assessing post-menopausal women, found that 82% of the patients had 25(OH)D levels considered insufficient. Several studies have reported a gradual decline of this vitamin's levels after menopause, which is more significant in older patients. Cauley et al.,¹⁹ in a study of over 90,000 post-menopausal women, observed a prevalence of low levels of 25(OH)D among these patients, as well as the subsequent increase in the risk associated with PFF, suggesting serum control in post-menopausal patients as method to investigate this risk.^{16,17,19-21}

Despite the predominance in females, males from the fracture group also presented serum levels considered insufficient (25.67 ng/mL) in the present study. In a prospective study of 1,608 elderly males, Cauley et al.²² demonstrated a significant increase in the risk of hip fractures in patients with low levels of 25(OH)D. The risk of fracture was significant only in male patients with deficient serum levels, which was associated with both PFF²³ and bone mineral density of the proximal femur.²⁴

In the present study, the association between vitamin D deficiency and the age variable was significant only in patients aged between 71 and 75 years ($p=0.003$) and over 80 ($p=0.003$). Ensrud et al.,²⁴ considering only the male population, found a significant association between bone loss and low levels of 25(OH)D among those aged over 75 years. Some authors consider that 25(OH)D levels could present an uneven distribution, characterized by a stable pattern after a certain age.¹⁷⁻¹⁹ In the present study, a division according to age of the patients was made in order to discriminate the risk in certain age groups. However, no other studies with this methodology were retrieved, hindering a proper comparison. The variable ethnicity presented an insufficient sample, a limitation also found by many authors in their analysis.^{19,25} Nevertheless, some authors consider that greater skin pigmentation due to genetic factors may be related to lower serum levels of vitamin D.^{12,19,25}

Chapuy et al.,⁸ in a classic clinical trial conducted in England, reported that the use of vitamin D3 associated with calcium led to a significant reduction in risk of fractures in elderly women that did not involve the spine when compared with a control group. Therefore, the prophylactic use of this

vitamin is recognized by many authors as an important factor in preventing fractures, especially PFF.¹⁻⁴

The main strength of the present sample was its considerable size of 341 patients. In the meta-analysis performed by Lai et al.,¹¹ of the 15 case-control studies with values of 25(OH)D considered significant in elderly PFF, only three showed a total sample higher than that of the present study. Even with a good sample, one bias of the present study was the non-seasonal characterization of the collection year, since sun exposure is known to be associated with levels of 25(OH)D, being relevant even in relation to the inadequate intake of this vitamin.¹¹ The time of serum collection of 25(OH)D, which was made at admission by transfer from another institution and showed variations, may also be considered a limitation of the present study. Furthermore, the study did not consider the clinical and metabolic situations presented by the patient who underwent the exam, such as changes in kidney or liver function, hormonal changes in thyroid function, and medication use, among others. However, despite representing sources of bias, such situations could constitute confounding factors to the various types of variables to be considered.^{10,11}

Conclusion

Lower levels of vitamin D3 were observed in elderly patients with PFF when compared with control patients without fracture. Significantly lower levels of this vitamin in female patients were observed in both groups. There was a significant association between the risk of this hypovitaminosis with PFF in the age ranges between 71 and 75 years and above 80 years. These findings demonstrate the important role of vitamin D3 in the outcome of PFF; its widespread use is suggested as a way to prevent this condition.

Conflicts of interest

The authors declare no conflicts of interest.

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