



Original Article

Associations of vitamin D deficiency with postoperative gait and mortality among patients with fractures of the proximal femur[☆]



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ABSTRACT

Objective: To assess whether serum vitamin D concentration is associated with gait status and mortality among patients with fractures of the proximal femur, six months after suffering the fracture.

Methods: Consecutive patients aged ≥ 65 years with fractures of the proximal femur, who were admitted to the orthopedics and traumatology ward of our service between January and December 2011, were prospectively evaluated. Clinical, radiological, epidemiological and laboratory analyses were performed, including vitamin D. The patients underwent surgery and were followed up as outpatients, with return visits 15, 30, 60 and 180 days after discharge, at which the outcomes of gait and mortality were evaluated.

Results: Eighty-eight patients were evaluated. Two of them were excluded because they presented oncological fractures. Thus, 86 patients of mean age 80.2 ± 7.3 years were studied. In relation to serum vitamin D, the mean was 27.8 ± 14.5 ng/mL, and 33.7% of the patients presented deficiency of this vitamin. In relation to gait, univariate and multivariate logistic regression showed that vitamin D deficiency was not associated with gait recovery, even after adjustment for gender, age and type of fracture (OR: 1.463; 95% CI: 0.524–4.088; $p = 0.469$). Regarding mortality, Cox regression analysis showed that vitamin D deficiency was not related to its occurrence within six months, even in multivariate analysis (HR: 0.627; 95% CI: 0.180–2.191; $p = 0.465$).

Conclusion: Serum vitamin D concentration was not related to gait status and/or mortality among patients with fractures of the proximal femur, six months after suffering the fracture.

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Associação da deficiência de vitamina D com mortalidade e marcha pós-operatória em paciente com fratura de fêmur proximal

R E S U M O

Palavras chave:

Vitamina D
Mortalidade
Marcha
Fraturas do fêmur

Objetivo: Avaliar se a concentração sérica de vitamina D está associada ao status de marcha e à mortalidade em pacientes com fratura de fêmur proximal seis meses após a fratura.

Métodos: Avaliados prospectivamente pacientes consecutivos com fratura de fêmur proximal, com idade ≥ 65 anos, internados na enfermaria de ortopedia e traumatologia do serviço, entre janeiro a dezembro de 2011. Foram feitas análises clínica, radiológica, epidemiológica e laboratorial, incluindo vitamina D. Foram submetidos à cirurgia e acompanhados ambulatorialmente em retornos 15, 30, 60 e 180 dias após a alta, quando foram avaliados os desfechos de marcha e mortalidade.

Resultados: Avaliados 88 pacientes. Dois foram excluídos por causa de fratura patológica. Oitenta e seis pacientes com idade média de $80,2 \pm 7,3$ anos foram estudados. Em relação à vitamina D sérica a média foi de $27,8 \pm 14,5$ ng/mL e 33,7% dos pacientes apresentavam deficiência dessa vitamina. Em relação à marcha, a análise de regressão logística uni e multivariada mostrou que a deficiência de vitamina D não esteve associada a sua recuperação, mesmo após ajuste por gênero, idade e tipo de fratura (OR 1,463; 95% IC 0,524-4,088; $p = 0,469$). Considerando a mortalidade, a análise de regressão de Cox mostrou que a deficiência de vitamina D também não esteve relacionada à sua ocorrência em seis meses, mesmo na análise multivariada (HR 0,627; 95% IC 0,180-2,191; $p = 0,465$).

Conclusão: A concentração de vitamina D sérica não esteve relacionada ao status de marcha e/ou à mortalidade em paciente com fratura de fêmur proximal seis meses depois dela.

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Introduction

The incidence of fractures of the proximal femur has increased over recent decades and there is an expectation that it will continue to increase because of the aging of the population.^{1,2} It is expected that by 2020, 16.3% of the American population and 25% of the Canadian population will be over the age of 65 years.² This increase in the numbers of elderly individuals will probably give rise to higher incidence and prevalence of diseases of the musculoskeletal system, such as fractures secondary to osteoporosis and osteoarthritis. According to Thorngren, the number of cases of hip fractures among patients over the age of 80 years has doubled over the last 20 years.³ According to Hu et al.,⁴ 1.5 million cases of hip fractures occur around the world and this number may reach 2.6 million in 2025 and 4.5 million in 2050.

Fractures secondary to bone fragility, especially those occurring in the proximal femur, have been correlated with significant reductions in independence and increased morbidity and mortality.⁵ According to Holt et al.,⁶ only 22% of the patients who, before the fracture occurred, were able to walk without support and unaccompanied recover this level of independence within the first 120 days after the event. This loss of independence is even more serious among patients over the age of 95 years: in this group, only 2% recover their preoperative ability to walk within the same period. Furthermore, the mortality rates relating to fractures of the proximal femur are very high and may range from 14% to 47% over the first year after their occurrence. All of these points emphasize the importance of and interest in recovering the ability to

walk and improving the prognosis, for patients with this type of fracture.⁶

Among the micronutrients relating to the risk of falls and fractures among elderly people, vitamin D can be highlighted. This is a liposoluble micronutrient with a function classically related to increased intestinal absorption of calcium, which participates in active transportation of this ion in enterocytes. It also participates in mobilizing calcium in bones, in the presence of PTH, and in increasing the renal reabsorption of calcium in the distal tubule.⁷ However, new functions have now been attributed to vitamin D. Studies have shown that it has an important role in modulating inflammatory and immunological processes, and that it may have a relationship with wound healing and with alterations to muscle mass and strength.^{8,9} Higher vitamin D concentrations have been correlated with lower fall rates among elderly patients. Consequently, this diminishes the risk of new fractures.¹⁰

The objectives of this study were to evaluate the demographic, clinical and biochemical characteristics of patients with and without vitamin D insufficiency and to ascertain whether the serum concentration of this nutrient is associated with walking status and with mortality among patients with fractures of the proximal femur, six months after the occurrence.

Sample and methods

The present study was approved by our institution's ethics committee and all the patients or the persons legally responsible for them signed a free and informed consent statement.

Consecutive patients of ages ≥ 65 years with fractures of the proximal femur who were hospitalized in the orthopedics and traumatology ward of our service between January and December 2011 were prospectively evaluated. The exclusion criterion was the presence of pathological fractures (secondary to neoplasia). All the patients underwent a surgical procedure to correct the fracture.

On admission, the patients' demographic data were registered. During the first 72 hours of their hospital stay, blood samples were collected for laboratory tests, including measurement of serum 25(OH) vitamin D3. Data relating to the type of fracture of the proximal femur (femoral neck, intertrochanteric or subtrochanteric fracture), length of the waiting time between hospital admission and surgery and duration of the operation were also recorded. The patients were followed up for up to six months after the occurrence of the fracture and were assessed in relation to postoperative walking status and mortality. These assessments were made on the first day after the surgical procedure, at the time of hospital discharge and at return visits 15, 30, 60 and 180 days after discharge. For patients who died before reaching 180 days, the walking status assessment of the last return visit was taken into consideration.

Vitamin D deficiency was characterized as a serum concentration lower than 20 ng/mL.¹¹ In relation to walking status, the patients were classified as walkers (who were walking with or without support = 1) and non-walkers (who were unable to walk = 0).

Laboratory assessment

The blood samples collected over the first 72 hours after the patient's admission were used for laboratory tests, including the vitamin D levels.

To produce a hemogram, an automated method in a Coulter STKS auto-analyzer was used, followed by confirmation of the morphological findings, platelet counts, leukometry and leukocyte differentials, by means of a conventional hematology method. To assay the sodium, potassium, magnesium, total calcium, glycemia, urea, creatinine, C-reactive protein and albumin levels, a dry chemical method was used (Ortho-Clinical Diagnostics Vitros 950®, Johnson & Johnson). Prothrombin time (PT) and activated partial thromboplastin time (APTT) were obtained using manual methods.

Determination of 25(OH) vitamin D3 in serum

The concentrations of 25(OH) vitamin D3 in serum were analyzed by means of high-performance liquid chromatography (HPLC). Initially, 150 μ L of serum was pipette into a glass flask; 200 μ L of precipitating reagent were added and the mixture was vortex-stirred for 30 seconds. Following this, 400 μ L of extraction reagent were added and the mixture was again vortex-stirred for another 30 seconds. It was then centrifuged for 10 min at 13,000 rpm. The supernatant was then transferred to another glass flask, evaporated with nitrogen, resuspended with 300 μ L of ethanol and stirred for another minute. Following this, 20 μ L were injected into the HPLC apparatus. After running this for 20 min, the column was left to stabilize so that a new reading could be made.

The equipment used was the isocratic HPLC with a manual Rheodyne injector and a 20 μ L loop. The analysis was performed in a 4 μ m silica column of dimensions 125 mm \times 4 mm (KC 3420RP; Immundiagnostik). The ultraviolet wavelength detector was set at 264 nm and the flow was set at 0.75 mL/min. The mobile phase was supplied by the manufacturer (Immundiagnostik). The internal standard used was from Sigma-Aldrich (C9774) and the control was from Chromsystems (25 [OH] vitamin D3 serum control, bi-level I+II). The test sensitivity was 2.5 μ g/L and the coefficient of variation was <7%.^{12,13}

Statistical analysis

The data were presented as means and standard deviations or as medians and 25th and 75th percentiles. The categorical variables were analyzed by means of the χ^2 or Fisher test. The continuous variables were analyzed using Student's t test when they presented parametric distribution or using the Mann-Whitney test when they presented nonparametric distribution. To assess whether the 25(OH) vitamin D3 levels were associated with recovery of the ability to walk 180 days after the fracturing, we used uni and multivariate logistic regression. In order to evaluate mortality, we used the Cox proportional hazards model. In the multivariate analyses, the variables were adjusted according to gender, age and type of fracture. The significance level was taken to be 5%.

Results

Eighty-eight consecutive patients with fractures of the proximal femur were evaluated. Of these, two were excluded because their fractures were pathological. Thus, 86 patients of mean age 80.2 ± 7.3 years were evaluated. Among these patients, 77% were women, 70% presented recovery of the ability to walk and 12.8% had died by the sixth month after the fracture event. In relation to serum vitamin D, the mean concentration was 27.8 ± 14.5 ng/mL and 33.7% of the patients presented deficiencies of this vitamin.

The demographic and clinical data on the patients according to their serum vitamin D concentrations are presented in Table 1. The majority of the patients hospitalized presented transtrochanteric fractures (55%) and fractures of the femoral neck (38%). The vitamin D concentration did not have any influence on the type of fracture. Moreover, vitamin D deficiencies did not present any associations with the clinical and demographic data on the patients evaluated (Table 1). The biochemical data are presented in Table 2. There were no differences regarding the laboratory test results between the groups with and without vitamin D deficiencies.

In relation to walking, the uni and multivariate logistic regression analyses showed that the vitamin D deficiencies did not have any association with recovery of the ability to walk (OR 1.212; 95% CI 0.451–3.252; $p = 0.703$), even after adjustment according to gender, age and type of fracture (OR 1.463; 95% CI 0.524–4.088; $p = 0.469$) (Table 3).

With regard to mortality, the Cox regression analysis showed that the vitamin D deficiencies also did not have any correlation with occurrences of mortality within the first six

Table 1 – Clinical and demographic variables of the patients with fractures of the proximal femur, according to their serum vitamin D concentration.

Variables	Serum vitamin D (25OH vit D3)		p value
	≥20 ng/mL (n = 57)	<20 ng/mL (n = 29)	
Age (years)	79.8 ± 6.7	81.0 ± 8.3	0.475
Female sex, n (%)	47 (82.5)	19 (65.5)	0.137
Preoperative hospital stay (days)	6 (4–8)	4 (3–7.5)	0.091
Duration of operation (min)	70 (50–90)	65 (50–90)	0.667
Type of fracture, n (%)			0.590
Femoral neck	24 (42)	9 (31)	
Transtrochanteric	29 (51)	18 (62)	
Subtrochanteric	4 (7)	2 (7)	
SAH, n (%)	37 (64.9)	14 (48.3)	0.210
DM type II, n (%)	14 (24.6)	6 (20.7)	0.895
Recovery of ability to walk, n (%)	39 (68.4)	21 (72.4)	0.894
Death, n (%)	6 (10.5)	5 (17.2)	0.497

Table 2 – Laboratory variables among the patients with fractures of the proximal femur, according to their serum vitamin D concentrations.

Variables	Serum vitamin D (25OH vit D3)		p value
	≥20 ng/mL (n = 57)	<20 ng/mL (n = 29)	
Hematocrit (%)	34.5 ± 6.2	34.0 ± 7.5	0.755
Hemoglobin (g/L)	12.1 (10.5–12.9)	11.9 (9.6–13.4)	0.924
Platelets ($\times 10^3/\mu\text{L}$)	206 (157–258)	196 (158–251)	0.756
Leukocytes ($\times 10^3/\mu\text{L}$)	8.200 (6.550–10.450)	7.700 (5.750–9.750)	0.267
PT	1.05 (1.0–1.13)	1.07 (1.04–1.14)	0.217
APTT	1.06 (0.93–1.18)	1.05 (0.97–1.22)	0.689
CRP (mg/dL)	5.2 (3.6–8.8)	4.6 (3.0–17.8)	0.491
Sodium (mmol/L)	138 (136–141)	139 (137–141)	0.745
Potassium (mmol/L)	4.1 (3.9–4.4)	4.2 (3.7–4.7)	0.701
Magnesium (mg/dL)	2.0 (1.8–2.1)	1.9 (1.7–2.1)	0.498
Total calcium (mg/dL)	8.78 ± 0.58	8.72 ± 0.61	0.625
Urea (mg/dL)	52 (36–72)	58 (39–75)	0.698
Creatinine (mg/dL)	0.80 (0.70–1.11)	0.80 (0.65–1.05)	0.528
Glycemia (mg/dL)	119 (95–150)	128 (97–146)	0.827
Albumin (g/dL)	3.22 ± 0.49	3.16 ± 0.50	0.585

months (HR 0.565; 95% CI 0.172–1.853; $p = 0.346$), even in the multivariate analysis (HR 0.627; 95% CI 0.180–2.191; $p = 0.465$) (Table 4).

Discussion

The increase in the size of the elderly population has been accompanied by the presence of events such as fractures of the proximal femur. After fractures have occurred, loss of independence, particularly with regard to returning to the pre-fracture walking status, is a frequent complication that often

brings devastating consequences for patients and their caregivers in relation to quality of life.⁶ Mortality may also occur. Thus, it becomes important to identify factors that might be associated with recovery of the ability to walk or with mortality. It has been suggested that the micronutrient vitamin D has potential effects on muscle strength and in relation to mortality. Thus, the present study compared demographic, clinical and biochemical parameters in patients with and without vitamin D deficiencies. In addition, the serum vitamin D concentrations were analyzed as potential predictors of recovery of the ability to walk or as predictors of mortality.

Table 3 – Logistic regression for predicting recovery of the ability to walk among patients with fractures of the proximal femur.

	Odds ratio	95% CI	p
Vitamin D < 20 ng/mL	1.212	0.451–3.252	0.703
Vitamin D < 20 ng/mL ^a	1.439	0.515–4.023	0.488
Vitamin D < 20 ng/mL ^b	1.463	0.524–4.088	0.469

^a Adjusted for gender and age.

^b Adjusted for gender, age and type of fracture.

Table 4 – Cox regressions for predicting mortality among patients with fractures of the proximal femur.

	Hazard ratio	95% CI	p
Vitamin D < 20 ng/mL	0.565	0.172–1.853	0.346
Vitamin D < 20 ng/mL ^a	0.639	0.189–2.163	0.471
Vitamin D < 20 ng/mL ^b	0.627	0.180–2.191	0.465

^a Adjusted for gender and age.

^b Adjusted for gender, age and type of fracture.

With regard to vitamin D deficiency, patients presenting concentrations lower than 20 ng/mL were compared with those whose concentrations were higher than this. The two groups presented the same demographic, clinical and biochemical characteristics. In fact, it is not known whether these concentrations are sufficient for non-classical actions of vitamin D. There is no consensus in the literature regarding what the normal serum vitamin D concentration would be, of in relation to the levels that would characterize deficiency and insufficiency of this micronutrient.¹⁴ These values have always been based on the relationship between vitamin D concentrations and disorders involving calcium homeostasis and fracture occurrences. With regard to the new functions described, the vitamin D concentration that is sufficient for action at these different sites has not yet been established.

In Canada, the International Osteoporosis Foundation has recommended that the serum vitamin D concentration should be greater than 30 ng/mL.^{15,16} On the other hand, the Institute of Medicine of the American National Academies has characterized vitamin D deficiency as serum concentration lower than 12 ng/mL and vitamin D insufficiency as concentrations between 12 and 20 ng/mL.¹⁷

In relation to recovery of the ability to walk, Cooper stated that fractures are related to a permanent incapacity rate of 30% with regard to activities of daily living and an incapacity rate of 40% with regard to walking independently.¹⁸ Larson et al.¹⁹ observed the functional recovery of patients with fractures of the proximal femur, among 607 patients. Among these participants, 446 had been able to walk independently without support before the surgery and 80% were found to have recovered their preoperative walking status one year after the surgery. Ekstrom et al.²⁰ found that only 55% of the patients with fractures of the proximal femur recovered their preoperative walking status, while 66% recovered their preoperative performance level with regard to activities of daily living. We put forward the hypothesis that the serum vitamin D concentration might influence this postoperative walking status. This was based on the functions most recently attributed to vitamin D. Classically, vitamin D has been correlated with maintenance of calcium homeostasis, but it has recently also been correlated with muscle contraction through intracellular calcium uptake and differentiation of myoblasts. This would diminish the incidence of falls and consequently the number of fractures.¹⁰ In patients with fractures, this would increase the chance of achieving better postoperative walking status. In our study, the serum vitamin D concentration did not show any correlation with the postoperative walking status, even in the corrected analysis.

With regard to mortality, the advent for surgical fixation of fractures of the proximal femur reduced this. However, since

then, it has remained stable at 25–30%.²¹ In our study, the rate was 12.8% within six months. The relationship between serum vitamin D concentration and mortality has been little studied. Some studies have shown that low serum concentration is associated with higher mortality in the general population and among elderly people.^{22–27} In a study with more than 180,000 participants, Saliba et al.²⁸ showed that the risk of death due to all causes was significantly higher among patients with low serum vitamin D concentration (lower than 50 nmol/L). In patients in whom the concentrations are lower than 30 nmol/L (deficiency), this risk becomes doubled. Thomas et al. showed that adequate vitamin D levels reduced mortality due to all causes and due to cardiovascular causes by 75% and 69%, respectively, among patients with metabolic syndrome.²⁹

In the literature, we found few studies that evaluated the serum vitamin D concentration and mortality among patients with fractures of the proximal femur. In a study that included 562 patients over the age of 70 years with these fractures, Madsen et al.³⁰ concluded that PTH and serum calcium were significantly associated with mortality, but not vitamin D concentration. Likewise, in our study, serum vitamin D concentrations did not show any association with mortality six months after the occurrence of fractures of the proximal femur.

Conclusion

In conclusion, in our study, serum vitamin D concentrations did not have any correlation with walking status or with mortality among patients with fractures of the proximal femur, six months after the event. The findings from this study emphasize that there is a need for further studies that might identify factors predictive of complications subsequent to fractures of the proximal femur.

Conflicts of interest

The authors declare no conflicts of interest.

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