Serum Levels of 25-Hydroxyvitamin D and Functional Recovery After Hip Fracture

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ABSTRACT. Di Monaco M, Vallero F, Di Monaco R, Mautino F, Cavanna A. Serum levels of 25-hydroxyvitamin D and functional recovery after hip fracture. Arch Phys Med Rehabil 2005;86:64-8.

Objective: To evaluate the association between serum levels of 25-hydroxyvitamin D ($25[OH]D_3$) and functional recovery after hip fracture.

Design: Cross-sectional study.

Setting: Rehabilitation hospital in Italy.

Participants: A total of 350 white hip-fracture patients consecutively admitted to a rehabilitation hospital. Thirty-five patients were excluded because their hip fracture was caused by major trauma or cancer affecting the bone or they could not complete rehabilitation.

Interventions: Not applicable.

Main Outcome Measures: Patients underwent $25(OH)D_3$ assessment at a mean $\pm$ standard deviation of 21.3 ± 8.1 days after the hip fracture. Functional recovery was evaluated by using Barthel Index scores.

Results: Low levels of $25(OH)D_3$ were found (median, 6.9ng/mL). By using the Spearman rank correlation test, a significant positive correlation was observed between serum $25(OH)D_3$ and Barthel Index score assessed on admission ($\rho = .218$, $P < .001$) and discharge ($\rho = .198$, $P < .001$), but not with the change in Barthel Index score attributable to rehabilitation. Linear multiple regression showed that the association between $25(OH)D_3$ and Barthel Index score was independent of 11 confounding variables: age, sex, hip-fracture type, pressure ulcers, cognitive impairment, neurologic impairment, infections, time between fracture occurrence and $25(OH)D_3$ evaluation, comorbidity, surgical procedure type, and previous hip fractures.

Conclusions: In the study population, serum $25(OH)D_3$ was an independent predictor of functional recovery assessed by Barthel Index score after hip fracture but not of the change in the functional score resulting from rehabilitation.

Key Words: Hip fracture; Osteoporosis; Rehabilitation; Vitamin D.

THE CRITICAL ROLE OF VITAMIN D in bone health is well established, as can be seen in the development of rickets in children and osteomalacia in adults, both of which result from the frank deficiency of the vitamin. Serum 25-hydroxyvitamin D ($25[OH]D_3$) is the best indicator of vitamin D status; the classic threshold defining vitamin D deficiency is 12ng/mL (30nmol/L). However, many studies indicate that even a less severe deficiency, called vitamin D insufficiency,[1] can impair bone health; it does not lead to frank osteomalacia, but it contributes to the genesis of osteoporosis, a multifactorial condition of low bone mass and microarchitectural disruption that results in fractures with minimal trauma.[2] Hip fracture is the most severe fragility fracture. It is associated with a significant increase in mortality, ranging from 10% to 30%.[3,4] Moreover, survivors of hip fracture have significant morbidity: only 40% fully regain their preinjury levels of independence.[5-8]

Low serum levels of $25(OH)D_3$ occur frequently in patients with hip fracture,[9,10] and 3 randomized controlled trials have shown that vitamin D (and calcium) supplements prevented fractures in the elderly.[11-14] As a consequence, the administration of calcium and vitamin D is recommended as baseline treatment for hip fracture prevention.[8,15] The effectiveness of vitamin D in preventing fractures could stem from its effects on muscle tissue in addition to its known effects on bone metabolism.[16] In various cross-sectional studies, low serum levels of $25(OH)D_3$ have been associated with reduced muscle strength and reduced ability to perform activities of daily living (ADLs) and mobility ADLs[10,17,18] and increased body sway and fall occurrences.[18-21] Low levels of $25(OH)D_3$ were not associated with general malnutrition, suggesting a specific role of the vitamin in muscle function.[18] Moreover, some clinical trials have shown that vitamin D supplementation in vitamin D-deficient subjects actually improved muscle strength, walking distance, and functional ability and decreased postural sway and the risk of falling,[22-26] although these data were not confirmed by a recent trial[27] and were in disagreement with a previous trial with 1,25-dihydroxyvitamin D.[28]

In the group of patients who recently sustained hip fractures, the prevalence of both vitamin D deficiency and poor restoration of function is high. Given the effects attributed to vitamin D on muscle health, it is intriguing to consider whether vitamin D depletion may affect the functional recovery after hip fracture, apart from enhancing the risk of hip fracture occurrence. Our aim was to evaluate the association between serum levels of $25(OH)D_3$ and functional recovery after hip fracture in a sample of elderly patients.

METHODS

Participants

We evaluated 350 white patients with hip fracture who had been admitted consecutively to our physical medicine and rehabilitation service from January 2001 to December 2002. We focused on white patients because few nonwhite elderly people live in Italy. Of the 350 patients, 14 were excluded because their hip fracture was caused by either major trauma or

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Table 1: Distribution of Barthel Index Scores, Change in the Barthel Index Scores Resulting From Rehabilitation, and the Serum Levels of 25(OH)D_3 in the 315 Patients

Barthel Index and Serum Levels	Mean ± SD	Median	Min	Max	IQR
Barthel Index					
At admission	41.8±16.9	45	0	80	25
At discharge	81.7±17.8	90	25	100	30
Change	39.9±13.7	40	5	90	15
25(OH)D_3 (ng/mL)	9.3±7.8	6.9	1.4	53.6	8.4

Abbreviations: IQR, interquartile range; Max, maximum; Min, minimum.

cancer affecting the bone. All 336 remaining patients suffered from fractures that were either spontaneous or caused by minimal trauma (trauma equal to or less than a fall from a standing position). Of these patients, 21 were excluded because they died or were transferred to other hospitals. The final study sample included 315 patients. None of the patients were being treated with either vitamin D or its derivatives.

Outcome Measures

The functional evaluation, both on admission to rehabilitation and at the time of discharge, was performed by an experienced physiatrist by using the Barthel Index (original version unchanged).[29] A blood sample was collected at a mean ± standard deviation (SD) of 21.3±8.1 days after hip-fracture occurrence and 25(OH)D_3 was assessed by an immunoenzymatic commercial assay.[a] Eleven variables were studied in each subject as prognostic factors: age, hip fracture type (cervical or trochanteric), sex, pressure ulcers (ulcers involving a break in the skin), cognitive impairment (Mini-Mental State Examination score, $<24/30$), neurologic impairment (impairment found at clinical examination because of neurologic diseases, mainly Parkinson's disease or stroke), infections (all the infections needing an antibiotic regimen during the length of stay [LOS]), time between fracture occurrence and 25(OH)D_3 evaluation, number of concomitant diseases, surgical procedure type (arthroplasty or internal fixation), and previous hip fractures.

Data Analysis

We investigated the linear correlations between 25(OH)D_3 and both Barthel Index score and the change in Barthel Index score resulting from rehabilitation. Because all the variables were nonnormally distributed (table 1), the Spearman rank correlation test was performed. Linear multiple regression analysis was performed and included the 11 prognostic factors listed earlier as well as the serum level of 25(OH)D_3 as independent variables and the Barthel Index score as the dependent variable. Because the Barthel index score was nonnormally distributed, area transformation was performed by using the formula $(r-1/2)/w$, where w is the number of observations and r is the rank. After computing area transformation of the dependent variables, the residuals were normally distributed in the regression models. The statistical package used was SPSS, version 10.[b]

RESULTS

Descriptive Statistics

Descriptive statistics (mean ± SD) for the patients included age (79.6±8.3y) and number of concomitant diseases (2.4±1.2). Eighty-eight percent of the patients were women (men, 12%). Fifty-four percent of the patients had sustained a trochanteric fracture (46% had a cervical region fracture); 50% had internal fixation surgery and 50% had arthroplasty. Thirty-six percent of the patients had pressure ulcers, 29% had cognitive impairments, 13% had concomitant neurologic impairments, and 8% (25/315 patients, 24 of whom suffered from contralateral hip fractures) had had a previous hip fracture. Fifty-one percent of patients suffered from at least 1 infection needing antibiotics during the LOS.

Correlation Between 25(OH)D_3 and the Barthel Index Score

A significant positive correlation was found between the serum levels of 25(OH)D_3 and the Barthel Index scores assessed at both admission (ρ=.218, $P<.001$) and discharge (ρ=.198, $P<.001$) (fig 1). The Barthel Index score increased after rehabilitation in the 315 patients (table 1). No significant correlations were found between 25(OH)D_3 serum levels and Barthel Index change score after rehabilitation (ρ=−.001).

Association Between 25(OH)D_3 and the Barthel Index Score

The percentage of the variance of the Barthel Index score accounted for by the independent variables was 24.8% before rehabilitation and 30.9% after rehabilitation. The association between the 25(OH)D_3 serum levels and the Barthel Index scores assessed on admission and discharge was significant after adjustment for the 11 confounding factors (table 2).

DISCUSSION

Serum Levels of 25(OH)D_3

Serum 25(OH)D_3 levels were very low in the study sample: the median value was 6.9ng/mL, and 75% (236/315) of the patients had levels below 12ng/mL, the threshold defining frank deficiency. The high prevalence of vitamin D deficiency we found in our patients is in agreement with the wider literature, although differences were reported across various populations.[9,30-32] Our results are very similar to those recently reported from an Italian study[10] that showed that 76% of the 700 elderly women investigated had serum levels of 25(OH)D_3 below 12ng/mL. Lack of vitamin D fortification of diary products in Italy undoubtedly accounts for the very high prevalence of vitamin D deficiency among women.

Factors Associated With the Barthel Index Score: The Role of 25(OH)D_3

Several factors were associated with Barthel Index score after hip fracture. Negative prognostic roles of cognitive impairment, advanced age, and pressure ulcers have already been reported.[33-40] Patients with neurologic impairment who fracture a hip were recently shown to have low Barthel Index scores before and after rehabilitation[41]; our results support this finding. The negative prognostic role exerted by the infections

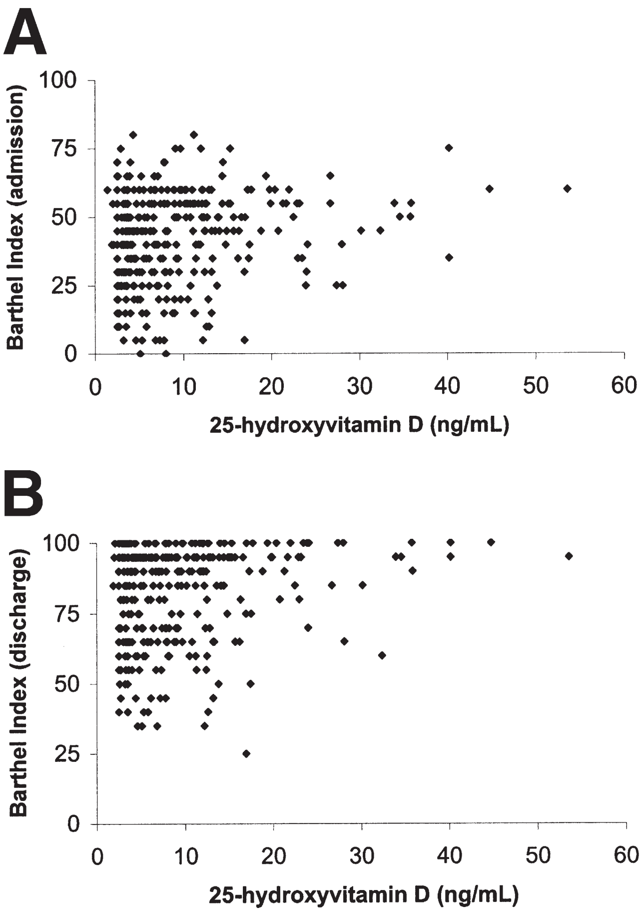

Fig 1. Scatterplot serum levels of 25(OH)D_3 and the Barthel Index scores in the 315 patients with hip fracture. By using the Spearman rank test, a significant positive correlation was found between 25(OH)D_3 and the Barthel Index scores assessed at (A) admission to rehabilitation (ρ=.218, P<.001) and (B) discharge from rehabilitation (ρ=.198, P<.001).

occurring during the LOS has also been reported.[41] On the whole, the set of variables included in multiple regression accounted for 24.8% and 30.9% of the variance of the Barthel Index score assessed on admission and discharge, respectively. We found a positive correlation between serum 25(OH)D_3 levels and Barthel Index scores. The correlation was significant both before and after rehabilitation, and it was independent of the 11 confounding variables evaluated. Conversely, serum 25(OH)D_3 did not correlate significantly with the change in Barthel Index score attributable to rehabilitation.

Study Limitations

Seasonal variations in 25(OH)D_3 levels were not investigated. However, because the study included patients admitted consecutively during a period of 24 months, the data were balanced for seasonal changes. Blood samples for 25(OH)D_3 assessment were collected at a mean of 21.3$\pm$8.1 days after hip fracture. The role of hospitalization in exacerbating the vitamin deficiency cannot be excluded, although a previous study[42] evaluating 25(OH)D_3 at different times after hip fracture did not show any meaningful influences exerted by hospitalization. We studied 315 patients who were admitted to a rehabilitation hospital in Turin (population, $\approx$1 million). We have no data about the possible selection criteria adopted by the orthopedic surgeons who sent the patients to the rehabilitation hospital, because no common rules were established. However, in Turin, almost all patients with a hip fracture are sent to rehabilitation hospitals. The study sample included white patients only. As a consequence, the data cannot be generalized to the larger population with hip fracture. Finally, some relevant prognostic factors, mainly prefracture health status, functional status, and mobility, were not investigated.

Mechanisms of the Association Between 25(OH)D_3 and Functional Recovery

The mechanisms underlying the association between 25(OH)D_3 and Barthel Index score were not investigated. Muscle biopsies obtained in osteomalacic patients showed type II muscle fiber atrophy. Several steps essential for muscle contraction (ie, calcium uptake in the sarcoplasmic reticulum, intracellular availability of both adenosine triphosphate and phosphate, and phosphate and protein synthesis, including the synthesis of actin and troponin) have been shown to be regulated by vitamin D.[16] So, muscle impairment caused by vitamin D deficiency may result in functional impairment after hip fracture.[43,44] Moreover, secondary hyperparathyroidism found in vitamin D–depleted subjects may contribute to impaired muscle function.[16] Interestingly, it was recently reported that femur bone mineral density (BMD) was positively associated with the Barthel Index scores after hip fracture in a sample of elderly women.[45] Our data suggest that vitamin D status may be the link between bone health and the functional recovery after hip fracture. Further studies assessing BMD, 25(OH)D_3, functional performance, and muscle strength in the same hip-fracture patients are needed to confirm this hypothesis.

Clinical Meaning of the Data

Vitamin D deficiency was extremely common in the study sample. We stress the importance of administering vitamin D after hip fracture in the elderly. This recommendation is in agreement with the clinical guidelines in the field[8] but is rarely followed in the current clinical practice.[46] Moreover, because

Table 2: Multiple Regression Analysis Models

Variables	β	P
Admission*		
Cognitive impairment	−.221	<.001
Age	−.259	<.001
Neurologic impairment	−.218	<.001
Pressure ulcers	−.122	.025
25(OH)D_3	.112	.038
Discharge†		
Age	−.296	<.001
Neurologic impairment	−.226	<.001
Cognitive impairment	−.211	<.001
Infections	−.208	<.001
25(OH)D_3	.118	.023

NOTE. The dependent variable was the Barthel Index (after normalization by area transformation). Among the independent variables, only those significantly associated with the Barthel Index score are listed in the table. Presence of cognitive impairment, neurologic impairment, pressure ulcers, and infections were conventionally attributed a value of 1 (the absence of the conditions listed above were attributed a value of zero).
*Dependent variable is Barthel Index at admission (R^2=.248, F=17.75, P<.001).
†Dependent variable is Barthel Index at discharge (R^2=.309, F=24.07, P<.001).

vitamin D deficiency is preventable, heightened awareness is necessary by physicians to ensure adequate vitamin D intake in the elderly. The positive correlation between serum levels of 25(OH)D_3 and functional recovery after hip fracture may indicate a new clinical meaning for 25(OH)D_3 assessment: prediction of functional recovery after fracture apart from the known role in the etiologic assessment of bone fragility. This role should be confirmed by prospective studies. Serum 25(OH)D_3 levels were not associated with postrehabilitation change in Barthel Index scores because of rehabilitation. Consequently, no advantages in functional prognosis related to rehabilitation can be expected from measuring serum 25(OH)D_3 after hip fracture. Our data suggest that an adequate vitamin D intake may improve the recovery after the fracture: preventing vitamin D deficiency may result in a reduction of both incidence of hip fractures and disability after fractures. However, this hypothesis needs to be confirmed by specifically designed intervention trials.

CONCLUSIONS

In elderly white patients who had sustained a hip fracture, serum levels of 25(OH)D_3 were very low. This finding stresses the importance of both preventing and treating vitamin D deficiency. We showed that serum levels of 25(OH)D_3 were positively correlated with Barthel Index scores assessed both before and after rehabilitation but not with the change in scores resulting from rehabilitation. Our data suggest that serum levels of 25(OH)D_3 may predict functional recovery after fracture. We hypothesize that ensuring adequate vitamin D intake in the elderly may result in reducing disability after hip fracture occurrence. This issue should be addressed by specific intervention trials. Conversely, assessment of serum levels of 25(OH)D_3 after fracture is not recommended for predicting change in functional status after rehabilitation.

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