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The Effect of High Doses of Vitamin D Replacement on Hospital Stay Length and Mobilization in Elderly Hip Fracture Patients

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Abstract

Objective: The widespread distribution of the vitamin D receptor across various tissues has expanded the understanding of vitamin D beyond its traditional role in calcium and bone metabolism. Severe vitamin D deficiency not only affects bone health but also impacts various aspects of the musculoskeletal system. This study aims to investigate the immediate postoperative benefits of high-dose vitamin D administration for hip fracture patients.

Methods: This study enrolled 85 consecutive patients aged over 60 years with hip fractures at our university hospital between 2013 and 2014. Patients were divided into 2 groups based on fracture location: pertrochanteric fractures in the osteosynthesis group and femoral neck fractures in the arthroplasty group. Each group was further divided based on preoperative vitamin D administration. Perioperative surgical parameters, length of hospital stay, early postoperative physical performance, and occurrence of delirium were recorded.

Results: The study included 85 participants undergoing bipolar hemiarthroplasty (n = 34) and proximal femoral nail (n = 51) procedures. No significant differences were observed in delirium incidence, operation duration, bleeding, or perioperative blood pressure between groups. Hemiarthroplasty patients receiving vitamin D showed improved 8-foot up and go test performance, while the proximal femoral nail group had shorter hospital stays. Delirium correlated with age and polypharmacy; however, the incidence of delirium was not influenced by vitamin D supplementation.

Conclusion: High-dose vitamin D supplementation significantly reduced hospital stays for osteoporotic proximal femur fractures treated with osteosynthesis using a proximal femoral nail. Vitamin D replacement also improved short-term physical performance in patients with femoral neck fractures treated with hemiarthroplasty. Vitamin D supplementation offers a safe and cost-effective adjunct therapy for the recovery of elderly patients from hip fractures.

Keywords: Vitamin D, osteoporosis, femoral neck fractures, pertrochanteric fractures, proximal femoral nailing, hemiarthroplasty

Introduction

Vitamin D is the mediator of the benefit that sunlight bestows upon the human body.[1] While vitamin D primarily regulates bone turnover and mineral metabolism, recent literature has shed light on the widespread distribution of its receptor and 1-alpha hydroxylase activity across various tissues, prompting researchers to explore its broader physiological effects beyond skeletal health.[2]

The chemical composition of vitamin D, characterized by its lipophilic nature and low molecular weight with a positive charge, grants it access to almost every tissue in the body, including the blood–brain barrier. Its various biological actions are primarily mediated by binding to the vitamin D receptor found in nearly all tissues and cells throughout the human body. Apart from its widely known function in bone mineral metabolism, the widespread distribution of vitamin D receptors explains its numerous potential benefits for hip fracture patients undergoing treatment with either arthroplasty or osteosynthesis. As such, vitamin D is implicated in immunomodulation by regulating inflammation and cytokines, as well as influencing cell proliferation, differentiation, apoptosis, and angiogenesis, alongside its essential role in muscle strength and contraction.[3,4]

The extraskeletal effects of 25-hydroxycholecalciferol (25-OH-D) in regulating crucial metabolic pathways suggest that low levels of 25-OH-D can lead to multiple organ dysfunction, disability, and compromised health stability.[4] These consequences contribute to the decompensation of concomitant metabolic issues, the necessity of polypharmacy, and prolonged hospital stays. One possible reason for the limited understanding and inconsistent observation of these pleiotropic benefits of vitamin D is that the blood levels required for these effects to manifest cannot be reliably achieved with current replacement regimens. Therefore, vitamin D replacement using acute high doses may be beneficial for both prompt repletion and the manifestation of pleiotropic effects.

Hip fractures impose a significant metabolic burden and functional loss on the elderly and often result from low-energy traumas in this age group.[5-7] Approximately 900 000 hip fractures are expected to occur each year in Europe, with 20% of these patients facing mortality due to either the primary trauma or related complications, many of which are preventable.[7,8] Vitamin D deficiency is highly prevalent in elderly hip fracture patients, with rates as high as 93.9% for insufficiency (25(OH)D < 30 ng/mL) and 71.7% for deficiency (25(OH)D < 20 ng/mL).[4,9] A recent large meta-analysis

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reported that high serum 25(OH)D levels reduce the risk of hip fractures in patients aged 60 years or older.[10] However, the effect of high doses of vitamin D replacement in the early postoperative period has not been evaluated in the literature.

The well-being of hip fracture patients in the early postoperative period is influenced by various factors, including wound healing, mobilization, cognition, and nutrition. A single inexpensive nutritional component that can improve these parameters would greatly facilitate the early discharge of these patients. Therefore, this study aims to investigate the effectiveness of acute high-dose vitamin D replacement in reducing postoperative complications, shortening hospital stays, and enhancing postoperative physical performance in hip fracture patients.

Methods

The study, conducted in accordance with the Declaration of Helsinki, received approval from the İstanbul University-Cerrahpaşa Ethical Committee for Clinical Studies (Approval no: 83045809/11281, Date: May 10, 2013), and written informed consent was obtained from all individual participants included in the study. A total of 85 consecutive patients (27 males and 58 females) aged over 60, presenting to the emergency department with a diagnosis of hip fracture, were enrolled. Exclusion criteria included primary hyperparathyroidism, advanced chronic kidney disease, malabsorption syndromes, sarcoidosis, hypercalcemia, and documented cognitive impairment. Patients were divided into 2 groups based on fracture location: pertrochanteric fractures (osteosynthesis group) and femoral neck fractures (arthroplasty group). Within each group, patients were randomized into 2 subgroups: those who received preoperative vitamin D supplementation (D+) and those who did not (D−). The supplementation group received a single oral loading dose of 300 000 IU (7.5 mg) cholecalciferol, followed by a daily dose of 1000 IU (25 mcg). No supplementation or placebo was given to the control group. Delirium was assessed daily using the delirium observation screening tool. Surgical treatment consisted of either proximal femoral nailing or bipolar hemiarthroplasty, according to fracture type, followed by inclusion in a standardized rehabilitation protocol. Time from admission to surgery, duration of hospital stays, and admission to the intensive care unit were recorded. Postoperative physical performance was evaluated on the third day using the 8-foot up and go test when patients were mobilized with support.

Statistical Analysis

The Number Cruncher Statistical System (NCSS) 2007 & Power Analysis and Sample Size (PASS) 2008 statistical software (Utah, USA) was utilized for statistical analyses. Descriptive statistical methods (mean, standard deviation, median, frequency, ratio, minimum, maximum) were employed in the evaluation of study data. For the quantitative data, the Student *t*-test was used in cases where the variables exhibited a normal distribution, while the Mann–Whitney *U* test was employed for variables not showing a normal distribution in 2-group comparisons.

In the comparison of qualitative data, Fisher's exact test, Fisher–Freeman–-Halton test, and Yates continuity correction test (Yates corrected Chi-square) were utilized. Spearman correlation analysis was employed for assessing relationships between parameters. Significance was evaluated at the $P < .01$ and $P < .05$ levels.

Results

Twenty-seven male and 58 female patients with a mean age of 80.9 ± 7.72 were enrolled. There were 34 patients in the arthroplasty group and 51 patients in the osteosynthesis group.

In the arthroplasty group, no significant difference was found between patients with or without vitamin D replacement in terms of the length of hospital stays, the length of surgery, perioperative blood pressure, or the amount of perioperative bleeding. However, the 8-foot up and go test results were significantly better in patients who received vitamin D replacement ($P < .05$). In the osteosynthesis group, no significant difference was found between patients with or without vitamin D replacement in terms of the length of surgery, perioperative blood pressure, the amount of perioperative

Table 1. The Length of Hospital Stay, 8 Foot Up and Go Test and Other Parameters Compared in the 2 Subgroups (Vitamin D+ and Vitamin D−) within the Arthroplasty Group

		Total (n = 34)	B (NO Vit D) (n = 17)	BD (D Vit+) (n = 17)	
		Mean ± SD (Median)	Mean ± SD (Median)	Mean ± SD (Median)	[a]*P*
Length of hospital stay (days)		11.97 ± 4.12 (11.5)	13.06 ± 4.60 (13.0)	10.88 ± 3.35 (10.0)	***.188***
Time from admission to surgery (days)		3.15 ± 1.48 (3.0)	3.24 ± 1.68 (3.0)	3.06 ± 1.30 (3.0)	***.818***
Time from surgery to discharge (days)		8.82 ± 4.02 (8.0)	9.82 ± 4.64 (9.0)	7.82 ± 3.11 (7.0)	***.231***
Lenght of operation (minutes)		61.62 ± 8.41 (60.0)	60.59 ± 8.82 (60.0)	62.65 ± 8.12 (65.0)	***.528***
Perioperative systolic blood pressure		121.24 ± 16.33 (120.0)	122.79 ± 21.03 (121.0)	119.48 ± 17.89 (118.0)	***.431***
Perioperative bleeding		204.41 ± 62.00 (200.0)	202.94 ± 75.97 (200.0)	205.88 ± 46.38 (200.0)	***.885***
8 foot up and go test at third postoperative day (seconds)		102.24 ± 10,40 (101.0)	105.94 ± 8.34 (105.0)	98.53 ± 11.15 (96.0)	***.026****
		n (%)	n (%)	n (%)	
Occurence of delirium	None	27 (79.4)	13 (76.5)	14 (82.4)	[b]***1.000***
	Yes	7 (20.6)	4 (23.5)	3 (17.6)	

[a]Mann–Whitney *U* test, [b]Fisher's exact test. *$P < .05$.
Patients with preoperative high-dose vitamin D supplementation in the arthroplasty group showed significantly improved performances in 8 foot up and go test. The length of hospital stay did not reach significance, despite mean shorter hospital stay lenght recorded in the vitamin D subgroup. SD, standard deviation; Vit D, vitamin D.

Table 2. The Length of Hospital Stay, 8 Foot Up and Go Test and Other Parameters Compared in the 2 Subgroups (Vitamin D+ and Vitamin D–) within the Osteosynthesis Group

		Total (n = 51)	PFN (NO Vit D) (n = 25)	PFND (Vit D +) (n = 26)	
		Mean ± SD (Median)	Mean ± SD (Median)	Mean ± SD (Median)	[a]*P*
Length of hospital stay (days)		13.27 ± 7.60 (10.0)	15.16 ± 8.07 (13.0)	11.46 ± 6.79 (9.0)	***.041****
Time from admission to surgery (days)		3.75 ± 2.72 (3.0)	4.24 ± 3.51 (3.0)	3.27 ± 1.56 (3.0)	***.535***
Time from surgery to discharge (days)		9.53 ± 7.29 (7.0)	10.92 ± 7.47 (8.0)	8.19 ± 7.00 (5.5)	***.056***
Lenght of operation (minutes)		52.75 ± 15.85 (50.0)	54.40 ± 20.73 (50.0)	51.15 ± 9.20 (50.0)	***.877***
Perioperative systolic blood pressure		118.76 ± 20.12 (124.0)	121.72 ± 17.43 (121.0)	115.46 ± 19.91 (119.0)	***.453***
Perioperative bleeding		69.61 ± 29.71 (50.0)	76.00 ± 37.83 (50.0)	63.46 ± 17.65 (50.0)	***.382***
8 foot up and go test at third postoperative day (seconds)		120.59 ± 11.53 (117.0)	123.48 ± 12.22 (120.0)	117.81 ± 10.31 (114.5)	[b]***.079***
		n (%)	n (%)	n (%)	
Occurence of delirium	None	40 (78.4)	19 (76.0)	21 (80.8)	[c]***.941***
	Yes	11 (21.6)	6 (24.0)	5 (19.2)	

[a]Mann–Whitney *U* test, [b]Student-*t* test, [c]Yates' continuity correction test.
*$P < .05$.
Patients with preoperative high-dose vitamin D supplementation in the osteosynthesis group showed significantly shorter mean length of hospital stay. The early postoperative physical performance of the patients evaluated using 8-foot up and go test showed a trend towards significance ($P = .079$) suggesting a possible association that may warrant further investigation.

bleeding, or the physical performance. Meanwhile, the length of hospital stay was significantly shorter in patients with vitamin D replacement ($P < .05$), with a trend towards a shorter period from surgery to discharge ($P = .056$) (Tables 1 and 2).

There was no significant difference between the 2 groups in terms of any demographic parameters including age, sex, body mass index, diabetes, hypertension, polypharmacy, or the type of anesthesia. The mean vitamin D levels were 10.29 ± 5.10 ng/mL in the arthroplasty group and 10.24 ± 4.15 ng/mL in the osteosynthesis group. Mean parathyroid hormone levels were 92.51 ± 36.51 pg/mL in the arthroplasty group and 96.31 ± 42.49 pg/mL in the osteosynthesis group. Majority of our patients (54%) had severe vitamin D deficiency (< 12 ng/mL) according to the recent update of Amrein et al.[11]

The incidence of delirium was similar in both groups, at 20.6% in arthroplasty group and 21.6% in osteosynthesis group, and no significant difference was recorded in subgroups that received vitamin D replacement. Ten patients in the osteosynthesis group and 4 patients in the arthroplasty group were admitted to the intensive care unit postoperatively and were discharged to the orthopedic ward within 24 hours.

Discussion

Our study's results align with the solid body of literature on the benefits of early high-dose vitamin D replacement in both mobilization and length of hospital stay. However, our hypothesis, proposing that acute high-dose vitamin D supplementation would prevent important complications such as delirium in hip fracture patients, has been rejected.

Previous studies demonstrated an association between preoperative vitamin D deficiency and postoperative cognitive dysfunctions, mainly delirium.[3,5,12] Considering the multifactorial etiology of delirium in elderly patients, including factors such as dehydration, electrolyte imbalance, polypharmacy, and sleep disturbances, it is possible that the effect of vitamin D restoration alone might be limited unless these contributing factors are adequately regulated. Our results did not support such an association despite the high percentage of severe hypovitaminosis D in our cohort. However, it complements existing evidence suggesting that acute replacement alone is not sufficient for reversing this phenomenon. Nevertheless, our study aligns with Chen's meta-analysis, identifying 2 major risk factors associated with delirium as older age and polypharmacy, as well as recording a longer length of stay in patients with delirium.[1]

A very high percentage (96.5%) of our study population exhibited vitamin D deficiency, with more than half (54%) experiencing severe deficiency, characterized by blood levels lower than 10 ng/mL. Nevertheless, controversies persist in the literature regarding whether vitamin D levels should be assessed. Many studies previously reported that vitamin D measurements do not reliably reflect patients' vitamin D status in cases of systemic trauma such as hip fractures or surgery.[5,13-16] Waldron et al[13] demonstrated that vitamin D acts as a negative acute phase reactant and its levels significantly decrease following elective hip surgery.[11] Binkley et al[14] have shown an acute depletion in blood vitamin D levels in the early postoperative period, that normalizes by the third postoperative week; thus, high doses of replacement should be avoided based on these perioperative levels. Reid et al[15] reported the highest decrease, with a mean acute reduction of 40% in vitamin D levels of their knee replacement patients, which persisted for several months. Barker et al[17] demonstrated in their study the role of interferon gamma in transforming 25(OH)D into its active form 1,25(OH)D, a fact that explains the acute decrease in plasma levels, which seems to be correlated with the severity of the inflammation. While the primary reasons for this phenomenon remain unclear, numerous potential explanations exist. These include hemodilution, decreased production and conversion by the liver, reduced synthesis of vitamin D-binding protein, higher consumption during systemic inflammation, and increased tissue demand and enhanced catabolism of metabolites. Regardless of the

underlying cause, acute replacement of documented vitamin D losses may offer benefits in mitigating the negative effects associated with decreased levels, such as maintaining immune function, supporting bone health, and preventing complications related to vitamin D deficiency.

The relationship between muscle strength and vitamin D levels has been previously discussed in the literature; however, the benefit of an early high-dose replacement on a patient's physical performance has never been documented.[18] Glareup reports that myopathy related to low levels of vitamin D can manifest even before biochemical evidence of bone disease, and the weight-bearing antigravity muscles of the lower extremity are the most affected muscle groups by this phenomenon.[19] Similarly, a very strong inverse association between 25(OH)D levels and sarcopenia was reported by Kim et al[20], in a very large cohort. Bischoff–Ferrari et al[2] demonstrated the presence of vitamin D receptors in human muscle cells and, furthermore, observed a significant decrease in the expression of these receptors with advancing age. The authors suggest that this finding may contribute, at least in part, to the age-related decline in muscle strength. Moreover, the down-regulation of vitamin D receptors with advancing age may suggest a need for higher vitamin D levels to achieve similar effects. Hao et al[21], reported the association between vitamin D deficiency and reduced mobility following hip fracture surgery. The authors documented that vitamin D levels below 12 ng/mL are associated with reduced ambulation on the 30th and 60th days after surgery. Our results support Hao's findings, suggesting that the benefit of vitamin D repletion on muscle function starts much sooner, in the early postoperative period.

Eight-foot timed up and go test (TUG) is a frequently utilized clinical test to assess a patient's strength, agility, and balance in a single task.[2223] Wilkinson demonstrated that the 8-foot up and go test showed the strongest correlation with the physical function of an elderly patient with rheumatoid arthritis.[24] Laflamme et al[25] indicated that the timed up and go test is a reliable clinical test that monitors the current physical status and predicts long-term physical function and prognosis of hip fracture patients. The authors demonstrated that the patients who performed the TUG test in under 58 seconds by the fourth day of surgery have 8-fold greater chance of returning to independent mobility. Similarly, Hao et al[21] utilized the 8-foot up and go test to document the delay in mobilization in their hip fracture patients with low vitamin D levels. Our findings support previous literature, showing enhanced balance and endurance in the vitamin D replacement group, as manifested by improved results in the 8-foot up and go test. We demonstrated that oral administration of high-dose vitamin D can promptly reverse the adverse effect of vitamin D insufficiency; however, this phenomenon was only visible in our hemiarthroplasty group. A possible explanation is that the limitation of weight-bearing in the osteosynthesis group is much more physically demanding and involves additional factors such as body weight or pain management, making the response to high-dose vitamin D administration less pronounced in this group. A trend towards significance in the osteosynthesis group ($P = .079$) suggests that further investigation or a larger sample size might be needed to draw more definitive conclusions.

The association between vitamin D status and the length of hospital stay in patients undergoing major orthopedic surgery has been previously documented. Maier et al[26] reported that the patients with vitamin D levels below 20 ng/mL stayed on average 4.3 days longer than patients with normal vitamin D levels, and the difference was statistically significant. Hélard et al[4] reported that the patients with hypovitaminosis D stayed in the acute care unit on average 3 days longer than their counterparts with normal vitamin D levels.[3] Furthermore, Matthews agreed that such an association exists and that it is dependent on the severity of vitamin D deficiency.[27] Similarly, Beauchet indicated vitamin D deficiency as a risk factor for long hospital stays. Recently, Lim et al demonstrated that low levels of vitamin D lead to longer hospital stays and decreased postoperative ambulatory status, findings are in line with our results.[4,28] Contrarily, Amrein et al[22] conducted a randomized controlled clinical trial reporting that acute ultra-high doses of vitamin D replacement failed to affect the length of hospital stay but reduced mortality in patients with serum levels below 12 ng/mL. A large meta-analysis conducted by Llombart et al[6] reported no significant association between vitamin D deficiency and patients' physical performance or the length of hospital stay, but poorer outcomes in quality of life and functional abilities during the follow-up period.[5] Our study found that vitamin D supplementation reduced the length of hospital stay, but this effect was only significant in the osteosynthesis group. Our study's discrepant findings compared to those of Amrein and Llombart may stem from variations in patient demographics and baseline vitamin D levels across study populations. Moreover, the length of hospital stay can be considered a non-specific parameter for monitoring the general wellness of a patient. It can define the point where a patient's functional recovery and metabolic status satisfy the clinician that the patient no longer requires admission. Thus, it can widely vary according to the aspects of different cultures or healthcare systems.

Few limitations of our study are noteworthy. First, we did not evaluate post-replacement vitamin D levels since our initial hypothesis was not built on a specific blood level to achieve but to the effect of the replacement itself. The variability in vitamin D metabolism among individuals necessitates multiple measurements until target blood levels are achieved. Considering the previously reported safety of ultra-high levels of vitamin D replacements, we utilized loading doses of 300 000 units and examined their clinical effects independent of individual blood levels.[10,22,29] The prompt response to high doses of vitamin D replacement has been previously reported in the literature.[10] Amrein et al[30] documented a mean 25 ng/mL increase within 48 hours using a single oral replacement of 540 000 IU without any complications or toxicity. Ingstad et al[12] recently reported that an acute single dose of 100,000 IU reduced orthopedic complications in hip fracture patients during the first 30 days after surgery.[11] Bacon et al[29] investigated the optimal replacement regimen for vitamin D in a double-blind randomized study and confirmed that ultra-high loading doses of 500 000 IU followed by monthly maintenance doses rapidly and safely normalize vitamin D levels in the elderly. These results align with our findings suggesting that serum vitamin D levels can be promptly corrected using ultra-high replacement doses, which dispenses the need for documenting a patient's response.

Conclusion

Our study highlights the potential benefits of a preoperative acute high-dose vitamin D replacement therapy for hip fracture patients. We found that vitamin D supplementation may contribute to improving physical performance and shortening hospital stays. Considering the low incidence of side effects and the wide safety margin associated with vitamin D supplementation, it could serve as a cost-effective and safe adjunctive therapy for elderly patients recovering from hip fractures. However, further research is warranted to fully elucidate the extent of vitamin D's impact on postoperative outcomes in this population.

Availability of Data and Materials: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethics committee approval was received for this study from the İstanbul University-Cerrahpaşa Ethical Committee for Clinical Studies (Approval no: 83045809/11281, Date: May 10, 2013).

Informed Consent: Written informed consent was obtained from participants who participated in this study.

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