See corresponding editorial on page 507.

Vitamin D deficiency is associated with reduced mobility after hip fracture surgery: a prospective study

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ABSTRACT

Background: Hip fractures are associated with a high rate of morbidity and mortality, and successful ambulation after surgery is an important outcome in this patient population.

Objective: This study aims to determine whether 25-hydroxyvitamin D [25(OH)D] concentration or the Geriatric Nutritional Risk Index (GNRI) is associated with mortality or rates of walking in a patient cohort after hip fracture surgery.

Methods: Patients undergoing hip fracture repair from a multisite study in North America were included. Mortality and mobility were assessed at 30 and 60 d after surgery. Serum albumin, 25(OH)D, and intact parathyroid hormone were measured. Patients were characterized according to 25(OH)D <12 ng/mL, 12 to <20 ng/mL, 20 to <30 ng/mL, or ≥30 ng/mL. GNRI was categorized into major/moderate nutritional risk (<92), some risk (92 to <98), or in good nutritional status (≥98).

Results: Of the 290 patients [aged 82 ± 7 y, BMI (kg/m^2): 25 ± 5], 73% were women. Compared with patients with <12 ng/mL, those with higher 25(OH)D concentrations had higher rates of walking at 30 d ($P = 0.031$): 12 to <20 ng/mL (adjusted OR: 2.61; 95% CI: 1.13, 5.99); 20 to <30 ng/mL (3.48; 1.53, 7.95); ≥30 ng/mL (2.84; 1.12, 7.20). In addition, there was also greater mobility at 60 d ($P = 0.028$) in patients with higher 25(OH)D compared with the reference group (<12 ng/mL). Poor nutritional status (GNRI <92) showed an overall trend to reduce mobility (unadjusted $P = 0.044$ and adjusted $P = 0.056$) at 30 but not at 60 d. There was no association of vitamin D or GNRI with mortality at either time.

Conclusions: Vitamin D deficiency (<12 ng/mL) is associated with reduced ambulation after hip fracture surgery, whereas GNRI also contributes to immobility but is a less reliable predictor. Mechanisms that can explain why vitamin D deficiency is associated with mobility should be addressed in future studies. *Am J Clin Nutr* 2020;112:613–618.

Keywords: albumin, elderly, functional status, geriatric, hip fracture, mobility, mortality, nutritional status, vitamin D

Introduction

Hip fracture is one of the most serious and severe injuries in seniors because of its consequences including immobilization and functional decline (1, 2). Recovering from hip fracture is not consistent between patients and often relates to reduced mobility. Several variables prior to fracture are associated with walking recovery, but it is still unclear which aspects of a geriatric assessment influence mobility. Many patients lose their independence during this time, leading to high rates of mortality and functional disability and healthcare expenses after hip fracture (3–7). Thus, understanding modifiable risk factors that can attenuate the risk of mortality and an inability to walk are important goals due to the increasing number of elderly and those with hip fracture.

Vitamin D_3 (cholecalciferol) is hydroxylated to 25-hydroxyvitamin D [25(OH)D] in the liver, and low concentrations

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Supplemental Table 1 and Supplemental Figure 1 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

De-identified data described in the manuscript may be made available for academic research upon request pending application and approval of a Data Use Agreement that is established between Rutgers University and the academic researchers' institution.

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Abbreviations used: FOCUS, Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair; GNRI, Geriatric Nutritional Risk Index; iPTH, intact parathyroid hormone; PTH, parathyroid hormone; 25(OH)D, 25-hydroxyvitamin D.

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of serum 25(OH)D (<20 ng/mL) are considered a risk factor for fracture (8) and are associated with worse outcomes (9, 10). Maintaining normal concentrations of vitamin D can positively affect a diverse array of body functions, such as muscle health and cognitive domains that could affect mobility and risk of falls (11–13). In addition, elevated circulatory parathyroid hormone (PTH) may contribute to poor outcomes (14). However, the classic inverse relation between 25(OH)D and PTH has many confounders and is not consistently found in the literature (14). This is one reason why 25(OH)D alone may predict an outcome when PTH will not predict that same outcome.

Another factor affecting postoperative outcomes is nutritional status. Underweight or malnourished patients are at higher risk of death in the first year after hip fracture surgery compared with normal-weight patients, even when controlling for age and comorbidities (15). Nutritional assessment scores have been developed as more reliable indicators of clinical outcomes than using body weight alone to estimate the risk of mortality and other poor outcomes after surgical procedures. For example, the Mini-Nutrition Assessment (16) has been used to predict the duration of hospital stays after fracture, whereas the Geriatric Nutritional Risk Index (GNRI) is specific for at-risk elderly medical patients to predict morbidity and mortality (17, 18). In the present study, the GNRI is used to assess whether poor nutritional status affects outcomes after hip fracture surgery in an older population. In addition, given that low circulating 25(OH)D is also a nutritional marker that has inconsistently been associated with outcomes after surgery, we sought to examine whether 25(OH)D or GNRI could predict outcomes in the same population.

Methods

This study was a secondary analysis in a subset of subjects enrolled in the Functional Outcomes in Cardiovascular Patients Undergoing Surgical Hip Fracture Repair (FOCUS) Trial from 47 sites in North America (19). The primary outcome was the rate of death or an inability to walk 10 feet (or across a room) without human assistance at follow-up. The FOCUS trial was a randomized trial designed to evaluate whether a liberal or restrictive RBC transfusion threshold affects mortality and walking ability in patients with cardiovascular disease or its risks who underwent hip fracture repair between 2004 and 2009 (19). In this study, we measured pre- and postoperative blood specimens to assess 25(OH)D and PTH and albumin. Inclusion criteria were limited to those patients who did not receive blood transfusion, had a pre- and postoperative blood draw, and were >65 years of age. After these exclusions, 290 patients remained in the study sample (**Supplemental Figure 1**).

The mobility and mortality status of patients were assessed by telephone call at 30 and 60 d after surgery. Patients were defined as immobile if they were unable to walk 10 feet or across the room without human assistance. A secondary outcome was all-cause mortality, which was determined by telephone call and confirmed by vital status of patients using the Social Security database, hospital or outpatient medical records, or vital status. For any discrepancies identified, this was addressed with hospital records or published obituaries (19). The study protocol was approved by the institutional review board at Rutgers University, New Brunswick.

Biochemical analysis

Blood samples were collected before surgery and 2 or 4 d after surgery, stored at the NIH repository, and transferred to Rutgers University for analysis. Serum 25(OH)D and intact PTH (iPTH) were measured using ELISA [25(OH)D: Eagle Biosciences; iPTH: ALPCO]. Serum albumin was measured using a colorimetric method (BioVision, Inc.). Standard reference materials from the National Institute of Standards and Technology and Vitamin D External Quality Assurance Scheme for total 25(OH)D were used as external standards in each batch analysis to improve the quality and consistency of measurements. The interassay CV% was 7.0–8.6% for 25(OH)D and 2.6–2.8% for iPTH. The intra-assay CV% was 3.2–6.9% for 25(OH)D and 3.7–6.1% for iPTH.

Serum 25(OH)D concentrations were categorized a priori as <12 ng/mL (deficient), 12 to <20 ng/mL (inadequate), and 2 categories of sufficiency (20 to <30 ng/mL and ≥30 ng/mL) according to the National Academy of Medicine (previously, the Institute of Medicine) (8). High iPTH was defined as concentrations >65 pg/mL. Albumin concentrations were used with body weight to calculate GNRI, as described previously (17). The patients were categorized into 3 standard nutritional risk groups using the GNRI score: major/moderate risk (<92), some risk (92 to <98), and no risk (≥98) (17).

Statistical analysis

Logistic regression was used to determine association of 25(OH)D or GNRI categories with mortality and walking ability outcomes with adjustments for potential confounders. The OR was analyzed as unadjusted and adjusted (age and sex). Student's *t* test or 1-factor ANOVA and chi-square test were used for continuous variables and categorical variables, respectively, to assess the association of demographic and biochemical measures with mortality and the ability to walk 10 feet across a room without human assistance. All variables that are significantly associated ($P < 0.05$) with outcomes are used as confounders and adjusted in the logistic regression comparison. ORs and 95% CIs are reported. Continuous variables are presented as means ± SDs; categorical variables are shown in percentages. Statistical analyses were performed using SPSS (IBM, version 24.0). A P value <0.05 was considered significant.

Results

A total of 290 elderly hip fracture patients (aged 82 ± 7 y, 73% women) were included in this study (**Table 1**). Fractures were at the femoral neck, intertrochanteric, and subtrochanteric regions. Forty-six percent of the patients had low concentrations of 25(OH)D (<20 ng/mL). Sixty-seven percent of the patients had at least some nutritional risk (GNRI <98), whereas only 3% had major nutrition-related risk (GNRI <82). In patients with low 25(OH)D (< 20 ng/mL; $n = 133$), most (73%) also had some nutritional risk (GNRI <98). Compared with the preoperative concentrations (Table 1), postoperative 25(OH)D (2–4 d later) decreased to 18.1 ± 7.7 ng/mL ($P < 0.001$), iPTH increased to 63.5 ± 42.7 pg/mL ($P < 0.02$), GNRI decreased to 85.6 ± 6.8 ($P < 0.001$), and albumin decreased to 3.0 ± 0.4 g/dL ($P < 0.001$). In addition, we did not find any relation of 25(OH)D with iPTH before or after surgery in this cohort.

TABLE 1 Baseline characteristics of patients[1]

	Values
Age, y	82 ± 7 (65–102)
Female sex, %	73
Caucasian race, %	93
BMI, kg/m^2	24.5 ± 4.7 (12.9–50.8)
<18.5 (underweight), %	6
18.5 to <25.0 (normal weight), %	54
25.0 to <30.0 (overweight), %	30
≥30 (obese), %	10
25-Hydroxyvitamin D, ng/mL	22.0 ± 9.6 (2.9–57.4)
<12, %	12
12 to <20, %	34
20 to <30, %	37
≥ 30, %	17
Intact parathyroid hormone, pg/mL	55.1 ± 44.3 (4.4–326.5)
≤65 (normal), %	74
>65 (high), %	26
Albumin, g/dL	3.7 ± 0.5 (2.2–5.1)
Geriatric Nutritional Risk Index	95.1 ± 7.7 (67.5–117.5)
<92 (major/moderate risk), %	34
92 to ≤98 (some risk), %	33
>98 (no risk), %	33
Fracture region, %	
Femoral neck	46
Intertrochanteric	51
Subtrochanteric	6
ASA score (out of 5)	2.9 ± 0.6 (1.0–4.0)

[1] Values are means ± SDs (range); $n = 290$. ASA, American Society of Anesthesiologists.

There were 43% and 30% of the patients who were unable to walk without assistance at 30 d and 60 d, respectively. Patients who could not walk at either 30 or 60 d were older (85 ± 7 y) than those who could walk (81 ± 7 y) ($P < 0.001$). In addition, those unable to walk had lower a 25(OH)D concentration (20.4 ± 9.0 ng/mL) compared with those who could walk (22.8 ± 9.7 ng/mL) ($P = 0.043$) at 60 d.

The 30- and 60-d mortality was 3% and 7%, respectively. Patients who died after surgery were older (88 ± 6 y) than those who were alive (82 ± 7 y) ($P < 0.05$). In addition, at 30 d after surgery, albumin concentrations were lower in those who died (3.3 ± 0.4 g/dL) than those who were alive (3.7 ± 0.5 g/dL) ($P = 0.009$). GNRI score was also lower in those who died than in those who remained alive (89.0 ± 7.5 vs 95.3 ± 7.7; $P = 0.017$) at 30 d.

Circulating preoperative 25(OH)D concentrations (**Table 2**) were associated with the rates of walking at 30 d in both unadjusted and adjusted analysis. Patients with 25(OH)D deficiency (<12 ng/mL) were used as the reference group. Compared with 25(OH)D <12 ng/mL, patients with concentrations ≥12 ng/mL had an increased rate of walking (56–64% vs 35%) and higher 25(OH)D was associated with increased rates of walking (mobility) for adjusted and unadjusted analysis ($P < 0.05$). Notably, the 12-to-<20 ng/mL category of 25(OH)D was also associated with greater mobility compared with the deficiency group (<12 ng/mL) at 30 d ($P = 0.043$). There was no association between 25(OH)D with mortality at either 30 or 60 d. In addition, there was no association between postoperative 25(OH)D categories and any outcomes at either time point.

When analyzing the association of GNRI with mobility, more patients were able to walk with a GNRI score between 92 and <98 compared with those who were at nutritional risk (<92) at 30 d in both unadjusted and adjusted models (unadjusted: 2.03; 95% CI: 1.14, 3.61; $P = 0.016$; adjusted: 2.05; 95% CI: 1.13, 3.71; $P = 0.018$) (**Table 3**). Also, those persons categorized with a GNRI <92 walked less than those with a GNRI ≥92 at 30 d ($P = 0.011$). GNRI had no association with mobility at 60 d and no association with mortality at either 30 or 60 d after surgery in this study (Table 3). When examining persons with both low 25(OH)D (<20 ng/mL) and a GNRI <98 compared with good nutritional status, there was no relation with mobility or mortality at follow-up (**Supplemental Table 1**).

In addition, there were no findings indicating that iPTH concentrations were associated with mobility or mortality. However, in patients with high iPTH (>65 pg/mL), mobility was reduced ($P = 0.002$) if they were also at nutritional risk compared with good nutritional status (Supplemental Table 1).

Discussion

With an aging population, hip fracture has become one of the major health concerns in the elderly, leading to functional deficits and reducing the quality of life. Successful ambulation and functional recovery after surgery are important outcomes in this patient population. However, even with improved surgical techniques, the recovery rate of ambulation and 1-y mortality rate remain the same over decades (5). Thus, it is important to examine factors that influence postoperative functional outcomes and mortality. Low 25(OH)D concentrations and malnutrition are common disorders in elderly patients with hip fracture and often occur together since both are complications of poor nutritional intake. In addition, the combination of low 25(OH)D and high iPTH adversely affects bone metabolism and is considered a risk factor for fracture, but less is known about the association with functional outcomes. Several studies (17, 20) indicate that poor nutritional status is an important factor for predicting postoperative outcomes, yet there has been no large prospective trial that specifically addresses important outcomes, such as mobility or death. Thus, in the present study, we examined serum samples in patients after hip fracture to determine whether circulating 25(OH)D, iPTH, or GNRI-determined nutritional status influenced short-term mobility and mortality after surgical repair. The findings in this study indicate that preoperative 25(OH)D concentrations were associated with short-term mobility. There was a trend for poor nutritional status to predict lower mobility at 30 d, and when combined with an elevated iPTH mobility was further compromised. None of the variables [25(OH)D, iPTH, or GNRI] showed an association with mortality.

Low circulating 25(OH)D is a predictor of fracture risk (8, 21, 22), but findings for an association with functional outcomes and mortality have been equivocal. A longitudinal study in elderly men (71 y of age with a median follow-up of 12.7 y) showed that low concentrations of 25(OH)D were associated with cardiovascular mortality (23). Pioli et al. (9) found that prefracture 25(OH)D concentrations <6 ng/mL and functional status together (but not alone) affected unassisted mobility at 3, 6, and 12 mo in hip fracture patients in Italy.

TABLE 2 Association between preoperative vitamin D status and outcomes after hip fracture surgery[1]

	Vitamin D concentration				
	<12 ng/mL	12 to <20 ng/mL	20 to <30 ng/mL	≥30 ng/mL	*P* overall
Ability to walk					
30 d, % who walk	35	56	64	58	
Unadjusted OR (95% CI)	—	2.30 (1.03, 5.17)	3.24 (1.45, 7.26)	2.57 (1.04, 6.36)	0.040
Adjusted OR (95% CI)	—	2.61 (1.13, 5.99)	3.48 (1.53, 7.95)	2.84 (1.12, 7.20)	0.031
60 d, % who walk	51	67	74	73	
Unadjusted OR (95% CI)	—	1.89 (0.86, 4.15)	2.70 (1.22, 5.95)	2.62 (1.05, 6.55)	0.079
Adjusted OR (95% CI)	—	2.67 (1.14, 6.25)	3.42 (1.46, 8.00)	3.67 (1.37, 9.82)	0.028
Mortality					
30 d, % who died	3	5	2	2	
Unadjusted OR (95% CI)	—	1.85 (0.21, 16.39)	0.64 (0.06, 7.30)	0.71 (0.04, 11.72)	0.582
Adjusted OR (95% CI)	—	1.44 (0.15, 13.58)	0.54 (0.04, 6.62)	0.52 (0.03, 9.22)	0.631
60 d, % who died	11	9	6	2	
Unadjusted OR (95% CI)	—	0.80 (0.23, 2.79)	0.46 (0.12, 1.72)	0.16 (0.02, 1.51)	0.304
Adjusted OR (95% CI)	—	0.56 (0.15, 2.08)	0.34 (0.08, 1.40)	0.11 (0.01, 1.05)	0.206

[1] $n = 290$ patients in 4 categories: <12 ng/mL ($n = 35$), 12 to <20 ng/mL ($n = 98$), 20 to <30 ng/mL ($n = 108$), ≥30 ng/mL ($n = 49$); ORs were determined by binary logistic regression analysis, unadjusted or adjusted for age and sex.

However, in a meta-analysis of older persons from 15 studies, vitamin D status or supplementation did not play a critical role in improving muscle strength and mobility (24), but these studies generally had higher 25(OH)D reference points than in the current study (24). Our findings indicate that 25(OH)D concentrations <12 ng/mL are associated with a reduced rate of walking after surgery. In addition, a postoperative 25(OH)D <12 ng/mL, unlike preoperative concentrations, did not predict outcomes. These findings suggest that the significantly lower 25(OH)D after surgery does not accurately reflect vitamin D status (25) and therefore should not be used to determine clinical or nutritional interventions. While this study did not examine the long-term effects of preoperative vitamin D status, at least 1 study indicates that very low concentrations also predict longer-term mobility (9). In addition, it is possible that free or bioavailable 25(OH)D may be a better predictor of postoperative outcomes than total 25(OH)D (26) and could be considered in a future study. In hip fracture patients with supplemental vitamin D_3 (cholecalciferol; 2000 vs 800 IU/d) and physical therapy (standard: 30 min/d or 60 min/d), extended physical therapy reduced falls, whereas higher vitamin D intake reduced hospital readmission but not falls (27). These authors concluded that using both treatments together could prevent the further reduction of health-related quality of life after 6 mo (28). The etiology of the poor mobility in patients with severe vitamin D deficiency is not clear and could be associated with direct effects on muscle or effects on cognition or other organ systems (11, 13). In other reported studies, patients with hyperparathyroidism and vitamin D deficiency have greater risk of 1-y mortality after surgery (29) and hyperparathyroidism is generally associated with impaired health in the elderly (30). However, circulating iPTH was not an independent predictor of mobility or mortality in this study. iPTH combined with some nutritional risk was detrimental to mobility.

TABLE 3 Association between preoperative nutritional status and outcomes after hip fracture surgery[1]

	Geriatric Nutritional Risk Index			
	<92 (high risk)	92 to <98 (some risk)	≥98 (no risk)	*P* overall
Ability to walk				
30 d, %	47	64	60	
Unadjusted OR (95% CI)	—	2.03 (1.14, 3.61)	1.67 (0.94, 2.95)	0.044
Adjusted OR (95% CI)	—	2.05 (1.13, 3.71)	1.57 (0.88, 2.82)	0.056
60 d, %	65	75	67	
Unadjusted OR (95% CI)	—	1.62 (0.87, 3.01)	1.11 (0.61, 2.02)	0.290
Adjusted OR (95% CI)	—	1.70 (0.89, 3.28)	1.02 (0.54, 1.19)	0.206
Mortality				
30 d, %	5	4	0	
Unadjusted OR (95% CI)	—	0.83 (0.22, 3.18)	0	0.962
Adjusted OR (95% CI)	—	0.82 (0.20, 3.31)	0	0.960
60 d, %	8	7	5	
Unadjusted OR (95% CI)	—	0.91 (0.32, 2.60)	0.64 (0.20, 2.03)	0.740
Adjusted OR (95% CI)	—	0.84 (0.28, 5.36)	0.68 (0.21, 2.25)	0.822

[1] $n = 290$ patients in categories of nutritional risk defined as follows: high risk, <92 ng/mL ($n = 97$); some risk, >92 and <98 ($n = 94$); no risk, >98 ($n = 99$). ORs were determined by binary logistic regression analysis, unadjusted or adjusted for age and sex.

Malnutrition in hip fracture patients is associated with a myriad of heath complications, rehabilitation time, and mortality (31). A low GNRI score reflects poor nutritional status and is used to estimate mortality in elderly populations (17,). The GNRI has been found to be an independent predictor of outcomes in elderly patients with congestive heart failure (32, 33), sepsis (34), and peritoneal dialysis (35, 36). While others have indicated that poor nutritional status using GNRI predicts mortality when the GNRI score is <92, indicating the need for an intervention (20), we did not show that GNRI was a reliable predictor of short-term mortality. This may be partially related to the low mortality and/or low incidence of major malnutrition in the current population. To our knowledge, the GNRI has not been used to predict mobility after hip fracture. However, another diagnostic tool, the Mini-Nutrition Assessment form, has shown that malnutrition is associated with reduced mobility in hip fracture patients in a Finnish population (37). Our findings indicate that GNRI tended to be associated with reduced mobility, when examining the overall *P* trend, and chi-square analysis indicates that persons with good nutritional status (>92) had greater mobility than those with poor nutritional status (<92). Because the combination of low 25(OH)D (<20 ng/mL) and at-risk nutritional status did not predict mobility, they may work independently of one another to negatively affect ambulation, but a larger study specifically designed to test this hypothesis is needed.

This study has a few strengths and limitations. One strength is the relatively large sample size using multiple samples of blood concentrations of 25(OH)D, iPTH, and albumin before and after surgery. In addition, the trial was conducted at 47 sites in the United States and Canada, enhancing its generalizability. However, a limitation in this study is its limited racial diversity, which is largely due to those at highest risk of hip fracture. Also, we only studied 1 arm of the parent study (those who did not need a blood transfusion) to be able to examine both pre- and postoperative blood variables, yet this limited the population to those who may have been relatively healthier (19). A strength is that the mortality in this sample is proportional to that in the original population (19). In addition, inclusion criteria in the original trial required the presence of cardiovascular disease or risk factors that may not reflect other populations, although most patients with hip fractures in this elderly age group typically have risk factors for cardiovascular disease.

This study provides new evidence that, when 25(OH)D concentration is >12 ng/mL, there is a higher rate of walking without human assistance at 30 and 60 d follow-up after hip fracture surgery. In addition, poor nutritional status in this population was less reliably associated with reduced mobility. Given the high prevalence of hip fracture surgery, and findings in the current study, addressing potential modifiable risk factors with treatment modalities to improve recovery should be explored in a future randomized controlled trial.

The authors' responsibilities were as follows—JLC and SAS: were responsible for study conception and design, and provided oversight; LH, YS, and SAS: conducted the data analysis; LH and SAS: drafted the manuscript; JLC: was responsible for the design of the original study; HN: was responsible for providing data from the original study; YS: consulted on statistical analysis and interpretation; JLC, HN, and YS: provided critical feedback on revisions; and all authors: provided critical revisions and read and approved the final manuscript. The authors report no conflicts of interest.

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