The Prevalence of Hypovitaminosis D in Patient with Fragility Hip Fracture at a Single Institution in Thailand

Suchat Phusunti MD*, Worasit Suthutvoravut MD*,
Aasis Unnanuntana MD, MSc*, Pojchong Chotiyarnwong PhD, MD*

** Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

Background: *The proportion of people aged 65 years or older continues to increase in Thailand. Consistent with that trend, the number of fragility fracture patients is increasing. Hypovitaminosis D is one of the important factors associated with fragility fracture.*

Objective: *To evaluate serum 25-hydroxyvitamin D (25(OH)D) level and prevalence of hypovitaminosis D in patients with fragility hip fracture in Thailand.*

Material and Method: *This study retrospectively reviewed 25(OH)D level in fragility hip fracture patients treated at Siriraj Hospital between January 2012 and December 2015.*

Results: *Three hundred seventy nine fragility hip fractures were included in this study. Two hundred sixty eight of those patients had serum 25(OH)D level available within one month after fracture. Mean age of patients was 80.8±8.3 years and 74.6% were women. One hundred twenty four patients (46.3%) had vitamin D deficiency (<20 ng/mL) and 86 patients (32.1%) had vitamin D insufficiency (20 to 30 ng/mL). Parathyroid hormone level was available in 159 of 268 patients, and 31.5% of those had hyperparathyroidism (PTH level >65 pg/mL).*

Conclusion: *Orthopedists who treat fragility hip fracture should always include treatment of vitamin D deficiency in their patient management plan. Future studies should establish treatment guidelines regarding dose and duration of vitamin D supplementation in fragility hip fracture patients.*

Keywords: *Hip fractures, 25-hydroxyvitamin D, Vitamin D deficiency, Hypovitaminosis D, 25(OH)D, Vitamin D insufficiency, Osteoporosis*

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Osteoporosis is one of the common health problems among the elderly in Thailand and worldwide[1,2]. Fragility hip fracture is one of the most common complications of osteoporosis. Fragility hip fracture is associated with significant increase in mortality rate after one year of fracture[3]. From a study conducted among patients in Chiang Mai, Thailand, Vaseenon et al reported 1-year and 10-year mortality rates after hip fracture of about 20% and 70%, respectively[4]. Estimated incidence of hip fracture in patients age more than 50-years-old in Asian countries ranges from 114 to 289 per 100,000 population[5]. In addition to the increment in morbidity and/or mortality in people who suffer fragility hip fracture, patient quality of life decreases and fracture treatment, and caregiver costs increase[6]. In osteoporosis patients, serum 25-hydroxyvitamin D (25(OH)D) level is one of the risk factors for fragility hip fracture[7,8].

Vitamin D is a fat soluble vitamin. It plays a role in the homeostasis of calcium and phosphorus, both of which affect bone health[9]. Vitamin D insufficiency leads to several complications, such as low bone mineral density, muscle weakness, muscle pain, postural imbalance; any or all of which are followed by increased risk of fall and potential hip fracture[10,11]. The two main sources of vitamin D are food and synthesis via sunlight exposure. Recent epidemiologic study in Thailand, where sunlight is plentiful year-round, found that about 45% of Thais have vitamin D level below 30 ng/mL[12]. Other studies from Asia found high prevalence of vitamin D deficiency in hip fracture patients that ranged from 76.7 to 96.7%[13-17]. However, data regarding the vitamin D status of fragility hip fracture patients in Thailand remains limited.

The objective of this study was to evaluate serum 25(OH)D level and prevalence of hypovitaminosis D in patients with fragility hip fracture in Thailand.

Correspondence to:
Chotiyarnwong P, Department of Orthopaedic Surgery, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkoknoi, Bangkok 10700, Thailand.
Phone: +66-2-4197968, Fax: +66-2-4128172
E-mail: pojchong.cho@mahidol.ac.th

Material and Method

Subjects

After receiving approval from the Siriraj Institutional Review Board, we conducted a retrospective chart review of all inpatients who were admitted at Siriraj Hospital with a diagnosis that involved hip fracture between January 2012 and December 2015 study period. The inclusion criteria were postmenopausal women or more than 50-year-old men with diagnosis of hip fracture (including femoral neck fracture and intertrochanteric fracture), and availability of patient serum 25(OH)D level. Patients were excluded for any one or more of the following reasons: hip fracture was not a fragility fracture (defined as any fracture that occurs spontaneously without high load, such as normal daily activities or falls from standing height or less)[18]; fracture caused by any other bone pathology, such as bone tumor; presence of any condition that could affect vitamin D metabolism, such as severe hepatic diseases (defined as serum alanine aminotransferase (ALT) >3 times upper limit of normal), history of current medication at the time of fracture containing vitamin D supplement >400 IU/day, and malabsorption syndromes, such as radiation enteritis, inflammatory bowel disease, and short bowel syndrome, and/or serum 25(OH)D level was measured later than one month after fracture.

Data collection

Patient demographic, clinical and laboratory data were collected from inpatient charts and recorded. Serum 25(OH)D level and all other laboratory investigations, including total calcium, phosphate, albumin, parathyroid hormone (PTH), blood urea nitrogen (BUN), and creatinine (Cr) were measured at the central laboratory of our hospital. Corrected serum total Ca was calculated from total serum calcium (mg/dL) + [(4.0 - serum albumin (g/dL)) x 0.8] for patients with an albumin level less than 4. Renal function was estimated by calculating the estimated glomerular filtration rate (eGFR, mL/minute/1.73 m^2) according to Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[19].

Vitamin D assay

Serum 25(OH)D was measured using electrochemiluminescence binding assay (ECLIA) on a cobas e411 analyzer (Roche Diagnostics GmBH, Mannheim, Germany). Intra-assay coefficient of variation percent (%CV) was 7.8% at 6.76 ng/mL and 1.7% at 67.0 ng/mL. Inter-assay %CV was 10.7% at 6.76 ng/mL and 2.2% at 67.0 ng/mL. Vitamin D levels were defined, as follows: deficiency = serum 25(OH)D level <20 ng/mL; insufficiency = serum 25(OH)D level 20 to 29 ng/mL; sufficiency = serum 25(OH)D level ≥30 ng/mL[20].

Statistical analysis

To determine an appropriate sample size, prevalence of vitamin D deficiency in fragility hip fracture patients was used as the primary outcome. Using the following formula, $n = Z^2_{(1-\alpha)}P(1-P)/d^2$; with $\alpha = 0.05$, allowable error (d) = 0.05 and rate of proportion (P) = 80% (0.8) (based on prevalence rate of vitamin D deficiency in hip fracture among Asian population), a sample size of at least 246 subjects was required for this study. At this sample size, the relative error (d/P) was calculated to be 6.3%.

Data analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). Data are shown as mean ± SD for normally distributed continuous variables and as median and interquartile ranges for not normally distributed variables and number and percentage for categorical variables.

Results

After retrospectively reviewing inpatient charts with a principal diagnosis of intertrochanteric fracture or femoral neck fracture, 379 cases were candidates for inclusion. After exclusions, 268 patients were included and analyzed. The average age of patients was 80.8±8.3 years and 74.6% of patients were female. Initial laboratory investigations and findings are shown in Table 1.

One hundred twenty four fragility hip fracture patients (46.3%) in this study had vitamin D deficiency (25(OH)D level <20 ng/mL) and 86 patients (32.1%) had vitamin D insufficiency (25(OH)D level between 20 and 29 ng/mL). Only 21.6% of patients had vitamin D level ≥30 ng/mL (Fig. 1). Approximately 60% of our patients had PTH level data (Fig. 2). A majority of those patients (around 2/3 of PTH level laboratory available) had PTH level in normal laboratory range (between 15 and 65 pg/mL). Fifty patients (31.4%) had PTH level >65 pg/mL. Of those, 11 patients (22%) had 25(OH)D level between 20 and 30 ng/mL and 32 patients (64%) had 25(OH)D level less than 20 ng/mL.

Discussion

Vitamin D insufficiency is common among the general population in Thailand[12] and incidence is

Table 1. Initial laboratory investigationsin patients with fragility hip fracture

Laboratory tests	Laboratory reference range	No. of patients	Mean ± SD*
Total calcium (mg/dL)	8.6 to 10.0	259	8.7±0.6
Corrected total calcium (mg/dL)	8.6 to 10.0	259	9.1±0.6
Albumin (g/dL)	3.5 to 5.5	266	3.5±0.5
Phosphorus (mg/dL)	2.5 to 4.5	236	3.3±0.8
Parathyroid hormone (pg/mL)	15 to 65	159	63.2±42.4
25(OH)D (ng/mL)	≥30	268	21.8±11.7
CTX (ng/mL)			
Female	0 to 0.45[30]	49	0.73±0.4
Male	0 to 0.36[30]	10	0.64±0.2
P1NP (ng/mL)	16 to 74	57	103.0±93.7
BUN (mg/dL)	6 to 20	268	19.7±10.4
Creatinine (mg/dL)			
Female	0.51 to 0.95	199	0.97±0.5
Male	0.67 to 1.17	68	1.72±1.7
eGFR (mL/minute/1.73 m^2)		205	61.6±23.7

25(OH)D = 25-hydroxyvitamin D; CTX = C-terminal telopeptide of type 1 collagen; P1NP = procollagen type 1 N-terminal propeptide; BUN = blood urea nitrogen; eGFR = estimated glomerular filtration rate
* Data is presented as mean ± standard deviation (SD)

even higher among people who have sustained fragility hip fracture[7,14-17,21]. Although human skin can synthesize vitamin D via ultraviolet B rays from sunlight, the majority of people in sunlight abundant areas like Thailand still have vitamin D insufficiency[12]. Low serum 25(OH)D concentration was shown to be associated with higher risk of hip fracture[7]. Accordingly, vitamin D supplementation is necessary to prevent new fracture in osteoporosis patients.

Measurement of vitamin D level is currently not widely available among hospitals in Thailand. The price of 25 (OH) D laboratory investigation is also high (approximately 1,000 Thai baht/35 USD), so vitamin D screening in the general population is not economically feasible. However, patients with fragility fracture are considered high-risk patients. As such, vitamin D level should be evaluated in this group of patients. From the cases retrospectively reviewed in

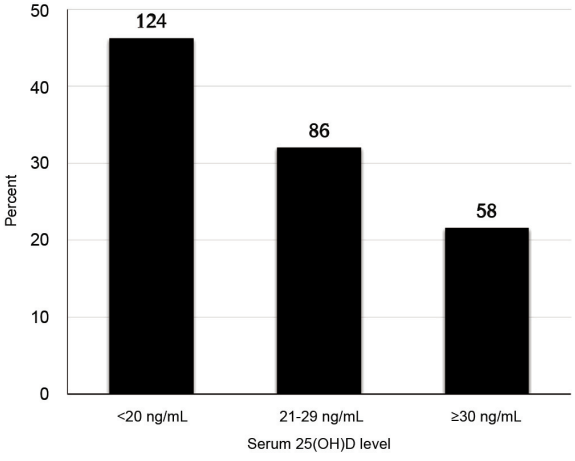

Fig. 1 Percentage of patients in each vitamin D insufficiency group when fragility hip fracture occurred (number of patients shown at the top of each bar).

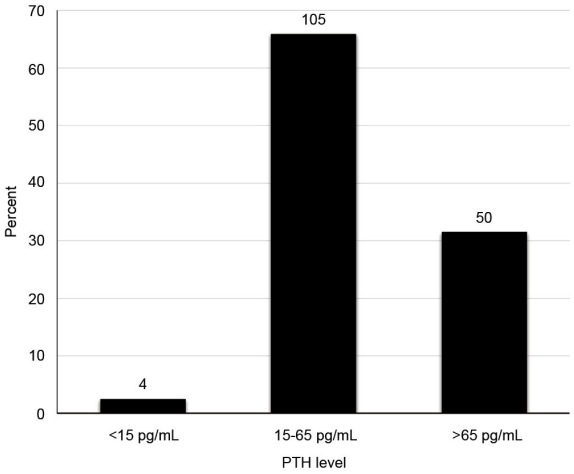

Fig. 2 Percentage of patients in each parathyroid hormone level group when fragility hip fracture occurred (number of patients shown at the top of each bar).

this study, two-thirds of fragility hip fracture patients treated at Siriraj Hospital had vitamin D insufficiency according to US Endocrine Society classification (25(OH)D <30 ng/mL) and one-third of patients showed increase in PTH level. Therefore, vitamin D supplementation should be prescribed in this group of patients.

Maintenance of sufficient vitamin D level is essential for maintaining musculoskeletal health and remains an important consideration in patients undergoing orthopaedic surgery[11,22,23]. While the Institute of Medicine (IOM) (United States) has proposed that a 600 IU daily dose of vitamin D3 is sufficient for bringing more than 97.5% of the population to the targeted 25(OH)D level of 20 ng/mL[24], the Endocrine Society issued a recommendation in 2011 that at least 1,000 IU of vitamin D3 intake per day is required to raise serum 25(OH)D level above 30 ng/mL[20]. Hypovitaminosis D can be treated using either vitamin D2 or vitamin D3 formulations. These two forms of vitamin D are chemically different and debate continues regarding whether vitamin D2 and vitamin D3 are equally effective in treating hypovitaminosis D. Some investigators have found similar effects of vitamin D2 and vitamin D3 on circulating 25(OH)D levels[25], while other studies have shown that vitamin D2 is less potent than vitamin D3 in maintaining serum 25(OH)D level[26-29]. Nevertheless, these two forms of vitamin D are currently considered interchangeable for purposes of increasing serum 25(OH)D level. In Thailand, vitamin D2 is the only form of vitamin D supplementation available for correcting low serum vitamin D level. It is currently available in 20,000 IU capsules only. For vitamin D supplementation, we recommend at least a double dose of the daily recommended dose of vitamin D for fragility hip fracture patients in cases where serum vitamin D laboratory testing is not available.

This study has some mentionable limitations. First, given the retrospective nature of this study, there exists a potential for bias in patient selection. Only 70% of fragility hip fracture patients in our series had initial 25(OH)D level measurement. Several patients also had missing laboratory values. Second, accurate information regarding patient dietary vitamin D intake (apart from the medical reconciliation form) and time of sunlight exposure for each patient were not available. However, the findings shown in this report reflect a real-world clinical setting, in that most of our hip fracture patients were elderly people who live in an urban area that may not have appropriate vitamin D supplementation and/or exposure to sunlight. Third, there was no record about a history of bisphosphonate use, which may affect the PTH level. However, from our metabolic bone disease (MBD) clinic registry, approximately 1/4 of patient in our clinic had a history of bisphosphonate used.

Conclusion

Vitamin D insufficiency is common in Thailand. Approximately 80% of fragility hip fracture patients had hypovitaminosis D. Of those 50% had vitamin D deficiency. Hyperparathyroidism was found in less than 1/3 of Thai fragility hip fracture patients. Vitamin D supplementation should be considered in these fracture patients. The development of a protocol that outlines appropriate dose and duration of vitamin D supplementation in fragility hip fracture is needed to reduce cost of 25(OH)D laboratory testing and to provide safe and effective vitamin D supplementation.

What is already known on this topic?

Vitamin D deficiency and secondary hyperparathyroidism are both common in hip fracture patients.

What this study adds?

While low serum vitamin D level was common in Thai fragility hip fracture patient, hyperparathyroidism was found in one-third of the subject population. Thus, calcium and vitamin D supplement should be given in this group of patients.

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Funding disclosure

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Potential conflicts of interest

None.

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สถานะของระดับวิตามินดีในผู้ป่วยกระดูกสะโพกเปราะบางหัก จาก 1 สถาบัน ในประเทศไทย

สุชัจจ์ ภู่สันติ, วรสิทธิ์ สุทัศน์วรวุฒิ, อาศิส อุนนะนันทน์, โพชฌงค์ โชติญาณวงษ์

ภูมิหลัง: *ปัจจุบันประเทศไทยกำลังก้าวเข้าสู่สังคมผู้สูงอายุ ปัญหาต่าง ๆ ที่พบบ่อยในผู้สูงอายุกำลังเพิ่มสูงขึ้น ภาวะกระดูกสะโพกเปราะบางหักเป็นหนึ่งในภาวะที่พบเพิ่มมากขึ้นเรื่อย ๆ ในปัจจุบัน ภาวะวิตามินดีต่ำเป็นหนึ่งในปัจจัยที่มีความเกี่ยวข้องกับการเกิดกระดูกหักในผู้สูงอายุจากภยันตรายที่ไม่รุนแรง*

วัตถุประสงค์: *เพื่อศึกษาระดับวิตามินดีในเลือดของผู้ป่วยที่มีกระดูกสะโพกหักในผู้สูงอายุจากภยันตรายที่ไม่รุนแรง*

วัสดุและวิธีการ: *การศึกษานี้ได้ทำการศึกษาย้อนหลังในผู้ป่วยที่มารับการรักษาภาวะกระดูกสะโพกเปราะบางหักที่โรงพยาบาลศิริราช ตั้งแต่วันที่ 1 มกราคม พ.ศ. 2555 ถึง 31 ธันวาคม พ.ศ. 2558 พบว่า จากผู้ป่วยที่มีกระดูกสะโพกหักทั้งหมด 379 ราย มีจำนวนทั้งสิ้น 268 ราย ที่ได้รับการเจาะเลือดเพื่อดูระดับวิตามินดีภายในช่วงระยะเวลา 1 เดือน หลังกระดูกหักจากผู้ป่วยทั้งหมดที่ได้รับการตรวจระดับวิตามินดี*

ผลการศึกษา: *ผู้ป่วยส่วนใหญ่เป็นเพศหญิง (200 ราย ร้อยละ 74.6) อายุเฉลี่ย 80.8±8.3 ปี มีผู้ป่วย 124 ราย (ร้อยละ 46.3) มีระดับวิตามินดีอยู่ในระดับที่ขาดวิตามินดี (น้อยกว่า 20 นาโนกรัมต่อมิลลิลิตร) 86 ราย (ร้อยละ 32.1) มีระดับวิตามินดีอยู่ในระดับต่ำ (ระหว่าง 20 ถึง 30 นาโนกรัมต่อมิลลิลิตร) โดยที่ค่าเฉลี่ยของระดับวิตามินดีขณะเกิดภาวะกระดูกเปราะบางหักอยู่ที่ 21.8±11.7 นาโนกรัมต่อมิลลิลิตร อย่างไรก็ตามจากจำนวนผู้ป่วยที่มีผลการตรวจระดับฮอร์โมนพาราไทรอยด์ พบว่ามีผู้ป่วยร้อยละ 31.5 มีระดับฮอร์โมนพาราไทรอยด์ที่สูงกว่าปกติ (สูงกว่า 65 พิโคกรัมต่อมิลลิลิตร)*

สรุป: *ในการรักษาผู้ป่วยกระดูกสะโพกเปราะบางหักควรให้การรักษาภาวะวิตามินดีต่ำร่วมไปด้วยในเวลาเดียวกัน โดยขนาดและระยะเวลาในการให้วิตามินดีเสริมที่ปลอดภัยและเหมาะสมสำหรับผู้ป่วยกลุ่มนั้นควรมีการศึกษาเพิ่มเติมในอนาคต*
