PREVALENCE AND RISK FACTORS OF VITAMIN D INADEQUACY AMONG THAI ELDERLY PATIENTS WITH OSTEOPOROTIC HIP FRACTURE

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Abstract

Background: Vitamin D deficiency directly impacts bone biology, eventually resulting in elevated risk of fragility fracture. Despite its global abundance, data concerning its prevalence and risk factors among Thai patients with osteoporotic hip fractures remains lacking.

Objectives: This study aimed to evaluate the average level of serum vitamin D, prevalence of hypovitaminosis D and its risk factor among Thai elderly patients with fragility hip fractures.

Methods: A cross-sectional study was conducted among Thai patients with fragility hip fractures aged 60 years or older in a single center from April 2016-April 2020. The patients were divided according to serum 25-hydroxy vitamin D (25-(OH)D) levels. Demographic data were compared to identify risk factors of vitamin D inadequacy.

Results: Of 258 patients, 74.81% were females with mean age of 78.76 years. The average serum 25(OH)D level was 19.64 ng/mL. Prevalences of vitamin D inadequacy, vitamin D insufficiency and vitamin D deficiency were 86.05, 28.69 and 57.36%, respectively. When compared with the vitamin D sufficiency group, the vitamin D inadequacy group had a history of frequent falls, higher body mass index (BMI) as well as high parathyroid hormone (PTH) levels. Risk factors associated with vitamin D inadequacy were BMI >23 kg/m2 (AOR= 4.67, 95%CI=1.24-17.73), and two or more falls within a year (AOR= 3.96, 95%CI=1.38-11.33). Moreover, risk factors associated with vitamin D deficiency were being female (AOR= 2.87, 95%CI=1.06-7.78), BMI >23 kg/m (AOR=7.20, 95%CI =1.67-31.02), two or more falls within one year (AOR=7.32, 95%CI =2.17-24.69) and elevated PTH level (AOR= 3.38, 95%CI=1.17-0.74).

Conclusion: Most elderly patients with fragility hip fractures had hypovitaminosis D. Risk factors included high BMI, frequent falls for vitamin D inadequacy, being female and high PTH levels for vitamin D deficiency. Serum 25(OH)D assessment and appropriate supplement are recommended, especially for patients with fragility hip fractures and aforementioned risk factors.

Keywords: Vitamin D inadequacy, Vitamin D deficiency, Risk factor, Fragility hip fracture

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Introduction

Fragility hip fracture is a common osteoporotic fracture with significant morbidity, leading to loss of independence, mortality and financial burden.[1, 2] As the society ages, incidence of fragility fracture increases. The adjusted incidence rate of hip fractures in Thailand has increased more than 31% from 1997 to 2006.[3] Despite advances in medical care, one-year mortality after hip fracture has increased from 18% in 1999 to 21% in 2007.[4]

Vitamin D deficiency is common among the elderly, especially among housebound and geriatric patients.[5] It directly impacts bone biology, causing secondary hyperparathyroidism, high bone turnover, bone loss, mineralization defects and result in a decrease in bone mineral density, and ultimately, fragility fractures.[6] While vitamin D inadequacy is abundant, it remains one of the modifiable risk factors of fragility hip fractures where physicians can easily fix to lessen osteoporotic fracture risk. A related study in Thai population estimated the prevalence of vitamin D deficiency of 78% among patients with fragility hip fractures [7] corresponding to a 2014 study in Singapore showing an even higher number of 92%. [8]

Apart from the aforementioned investigations, data on vitamin D sufficiency among patients with osteoporotic fragility hip fractures remain limited, particularly in Asian populations.[9] Moreover, no research in Thailand has published risk factors of vitamin D inadequacy among patients with fragility hip fracture from osteoporosis. Therefore, in this study, we aimed to investigate the prevalence of vitamin D inadequacy and to identify risk factors associated with vitamin D inadequacy among Thai patients with fragility hip fractures.

Methods

Participants

Upon approval of the institutional ethics committee (COA No.89/2018), a cross-sectional study was conducted among patients admitted to the Police General Hospital, Thailand between April 1, 2016 and April 30, 2020. The inclusion criteria were patients aged 60 years or more with fragility hip fractures from a low energy trauma defined as a fall from standing height or less. The exclusion criteria were patients with pathologic fractures from skeletal tumor or malignancy, bone metastasis, metabolic bone diseases, long term use of oral steroid or other medical conditions that would affect bone quality, as well as patients whose serum 25-hydroxy vitamin D (25(OH)D) levels were unavailable for the study.

According to a study on hypovitaminosis D among patients with fragility hip fractures in Singapore (8), the percentage of vitamin D inadequacy was 92%. The proportion (p) of 0.92 was used to calculate, resulting in a required sample size of at least 114 for this study.

Using serum 25(OH)D level, patients were divided in three groups according to the Endocrine Society's definition. (10) Vitamin D sufficiency was defined as having serum 25(OH) D of 30 ng/mL or higher. Values of serum 25(OH) D below 30 ng/mL were defined as vitamin D inadequacy which was subdivided in vitamin D insufficiency with 25(OH)D level of 20 to less than 30 ng/mL and vitamin D deficiency with 25(OH)D level below 20 ng/mL. Demographic data were compared across groups to identify risk factors for each level of hypovitaminosis D.

Data acquisition

Patient demographic data and laboratory results were collected from the electronic database, including age, sex, body mass index (BMI), underlying diseases, previous fractures, pre-injury status, previous osteoporotic medications and any possible causes of secondary osteoporosis. Laboratory investigations included serum levels of 25(OH)D, parathyroid hormone (PTH), calcium, phosphate, albumin, creatinine and alkaline phosphatase including estimated glomerular filtration rate. Blood collection was performed within two days after admission. Serum 25(OH) D level was measured using electrochemiluminescence binding assay (ECLIA) on a Cobas e601 Analyzer (Roche Diagnostics Germany). All other laboratory investigations were performed at the central lab center, Police General Hospital using the same standardized machine and technique.

Statistical analysis

All statistical analysis was performed using STATA, Version 15 and statistical significance was set at $p<0.05$ with 95% confidence interval (95%CI). Chi-square test and Fisher's exact test were used to compare categorical variables. Student's t-test was applied for continuous data. Multivariate logistic regression analysis was also performed to assess independent risk factors associated with hypovitaminosis D.

Results

A total of 274 patients with hip fractures were admitted at the Police General Hospital during the study period. Twelve were excluded due to the lack of sufficient data of serum 25(OH) D levels. Another four were excluded because the fractures proved to have pathologic evidence. The remaining 258 patients were enrolled in this study. The majority of patients (74.81%) were females. The study population flow diagram is demonstrated in **Figure 1.** The mean age was 78.76 years and mean BMI was 21.52 kg/m^2. The mean serum 25(OH)D level was 19.64 ± 10.55 ng/mL.

The patients were divided in two groups according to their vitamin D status, 36 (13.95%) had sufficient 25(OH)D levels while the remaining 222 (86.05%) had vitamin D inadequacy. They were further classified in 74 (28.69%) with vitamin D insufficiency and 148 (57.36%) with vitamin D deficiency. The prevalence of each category is shown in **Figure 2**.

Of 193 women, 170 (88.09%) had vitamin D inadequacy. Fifty-two of 65 (80%) men had vitamin D inadequacy. A numerically higher percentage of women were found in the vitamin D inadequacy group, but without statistical significance. Comparing among age groups (60 to 69, 70 to 79 and ≥ 80 years old), no difference was observed in the proportion of vitamin D inadequacy to vitamin D sufficiency. The average BMI in the vitamin D inadequacy group was significantly greater than that of the vitamin D sufficiency group (21.73 ± 3.84 kg/m2 vs. 20.19 ± 2.72 kg/m2, p=0.022) with a significant tendency towards being overweight. Serum PTH level was significantly lower in the vitamin D sufficiency group (67.00 ± 43.09 pg/mL vs. 48.94 ± 30.31 pg/mL, p=0.012). Patients in the vitamin D inadequacy group fell more often than those observed in the vitamin D sufficiency group (two or more falls within one year 39.64% vs. 16.67%, p = 0.016). The characteristics of the patients comparing between the vitamin D sufficiency and inadequacy groups are shown in **Table 1**.

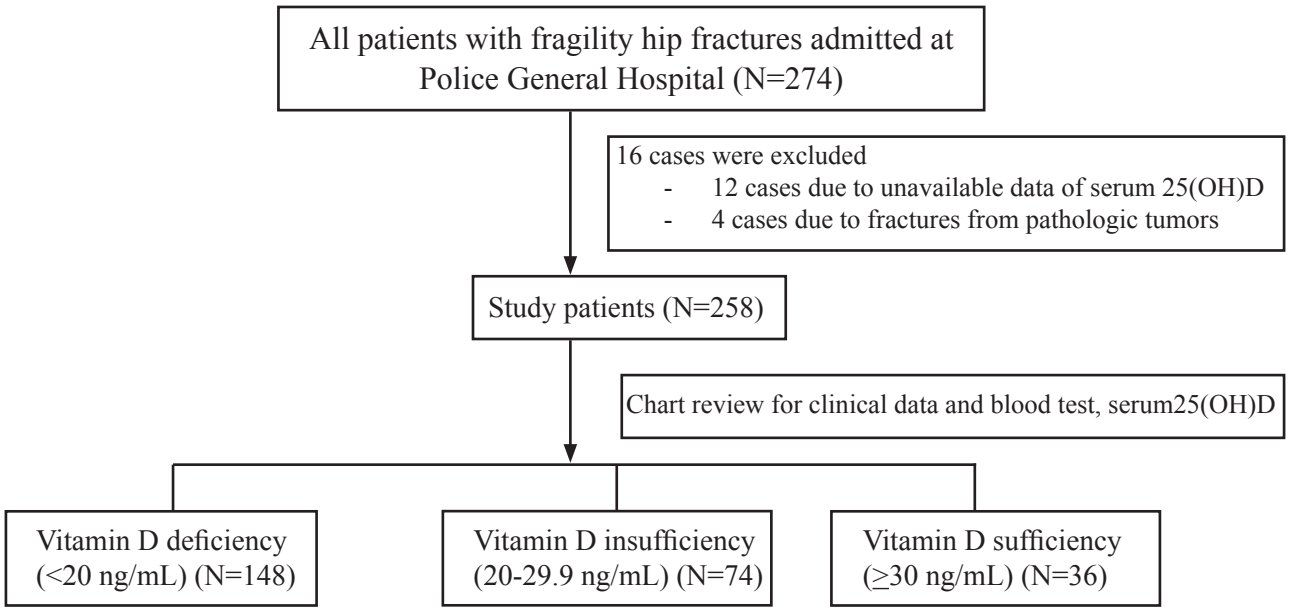

Figure 1. Flow diagram of study population

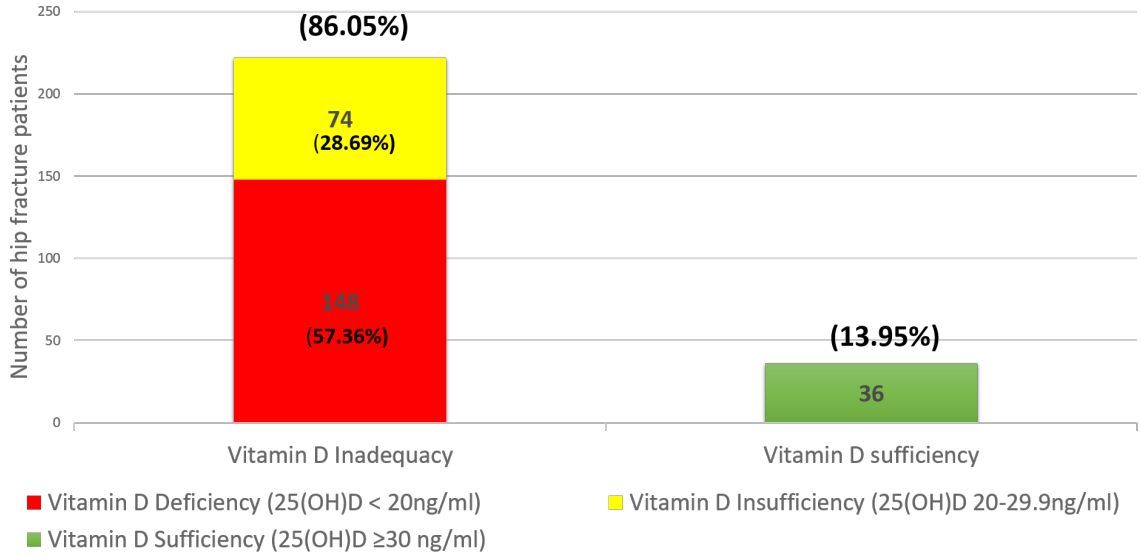

Figure 2. Prevalence of vitamin D sufficiency, vitamin D inadequacy (insufficiency and deficiency) among patients with fragility hip fractures
25(OH)D = 25-hydroxy vitamin D

Table 1. Characteristics of the cohort of patients with fragility hip fractures, patients with vitamin D inadequacy and vitamin D sufficiency. The variables were compared between vitamin D inadequacy and vitamin D sufficiency groups.

Characteristics	**Total** (n=258)	**Vitamin D inadequacy** (n=222)	**Vitamin D sufficiency** (n=36)	***p*-value**
Gender				
Female	193 (74.81%)	170 (76.58%)	23 (63.89%)	
Male	65 (25.19%)	52 (23.42%)	13 (36.11%)	0.104
Age (year)				
Mean ± SD	78.76 ± 8.86	79 ± 8.71	77.28 ± 9.71	0.281
60-69	36 (13.95%)	32 (14.41%)	4 (11.11%)	
70-79	93 (36.05%)	77 (34.68%)	16 (44.44%)	
≥80	129 (50%)	113 (50.90%)	16 (44.44%)	0.564
BMI (kg/m^2)				
Mean ± SD	21.52 ± 3.74	21.73 ± 3.84	20.19 ± 2.72	0.022*
<18.5	48 (18.61%)	39 (17.57%)	9 (25%)	0.040*
18.5-22.9	136 (52.71%)	113 (50.90%)	23 (63.89%)	
≥23	74 (28.68%)	70 (31.53%)	4 (11.11%)	
Underlying disease				
Hypertension	187 (72.48%)	165 (74.32%)	22 (61.11%)	0.100
Type 2 diabetes mellitus	99 (38.37%)	88 (39.64%)	11 (30.56%)	0.298
Previous fracture	28 (10.85%)	24 (10.81%)	4 (1.55%)	0.957
Pre-injury ambulation with gait aid	97 (37.60%)	83 (37.39%)	14 (38.89%)	0.863
Two or more falls within a year	94 (36.43%)	88 (39.64%)	6 (16.67%)	0.008*

Table 1. (continued)

Characteristics	Total (n=258)	Vitamin D inadequacy (n=222)	Vitamin D sufficiency (n=36)	*p*-value
Previous vitamin D supplement	32 (12.40%)	26 (11.71%)	6 (16.67%)	0.403
PTH level (pg/mL)	65.20 ± 42.01	67 ± 43.09	48.94 ± 30.31	0.016*
Albumin (g/dL)	3.83 ± 0.45	3.82 ± 0.46	3.91 ± 0.41	0.270
eGFR (ml/min/1.73 m^2)	66.44 ± 24.08	66.25 ± 24.74	67.60 ± 19.77	0.756

Values are presented as mean ± standard deviation or number (%)
BMI = body mass index; PTH = parathyroid hormone; eGFR = estimated glomerular filtration rate.
*$p < 0.05$ is statistically significant.

Table 2. Characteristics of the cohort of patients with fragility hip fractures, patients with vitamin D deficiency, and vitamin D sufficiency. The variables were compared between vitamin D deficiency and vitamin D sufficiency groups.

Characteristics	Total (n=184)	Vitamin D deficiency (n=148)	Vitamin D sufficiency (n=36)	*p*-value
Sex				
Female	145 (78.80%)	122 (82.43%)	23 (63.89%)	
Male	39 (21.20%)	26 (17.57%)	13 (36.11%)	0.015*
Age (year)				
Mean ± SD	78.30 ± 9.22	78.55 ± 9.12	77.28 ± 9.71	0.460
60-69	29 (15.76%)	25 (16.89%)	4 (11.11%)	
70-79	68 (36.96%)	52 (35.14%)	16 (44.44%)	
≥80	87 (47.28%)	71 (47.97%)	16 (44.44%)	0.555
BMI (kg/m^2)				
Mean ± SD	21.70 ± 3.98	22.07 ± 4.16	20.19 ± 2.72	0.011*
<18.5	33 (17.93%)	24 (16.22%)	9 (25%)	0.01*
18.5-22.9	94 (51.09%)	71 (47.97%)	23 (63.89%)	
≥23	57 (30.98%)	53 (35.81%)	4 (11.11%)	
Underlying disease				
Hypertension	132 (71.74%)	110 (74.32%)	22 (61.11%)	0.114
Type 2 diabetes mellitus	75 (40.76%)	64 (43.24%)	11 (30.56%)	0.165
Previous fracture	19 (10.33%)	15 (10.14%)	4 (11.11%)	0.863
Pre-injury ambulation with gait aid	77 (41.85%)	63 (42.57%)	14 (38.89%)	0.688
Two or more falls within a year	75 (40.76%)	69 (46.62%)	6 (16.67%)	0.001*
Previous vitamin D supplement	26 (14.13%)	20 (13.51%)	6 (16.67%)	0.626
PTH level (pg/mL)	67.77 ± 45.51	72.35 ± 47.46	48.94 ± 30.31	0.005*
Albumin (g/dL)	3.80 ± 0.46	3.77 ± 0.47	3.91 ± 0.41	0.103
eGFR (ml/min/1.73 m^2)	66.59 ± 25.17	66.35 ± 26.37	67.60 ± 19.77	0.790

BMI = body mass index; PTH = parathyroid hormone; eGFR = estimated glomerular filtration rate.
*$p < 0.05$ is statistically significant.

Table 2 demonstrates characteristics of patients with fragility hip fractures having vitamin D deficiency and vitamin D sufficiency. No difference was observed in the proportion of vitamin D deficiency to vitamin D deficiency among age group. The mean BMI was higher in the deficiency group (22.07 ± 4.16 kg/m^2 vs. 20.19 ± 2.72 kg/m^2, p=0.011). Patients reported two or more falls within one year in the vitamin D deficiency compared with the vitamin D sufficiency groups (46.62% vs. 16.67%, p=0.001). History of a previous fractures, previous injury ambulatory status, and previous vitamin D prescription did not differ between groups. The mean level of PTH in the vitamin D deficiency group was 72.35 pg/mL which was significantly higher than that found in the sufficiency group (48.94 pg/mL, p=0.005). Other laboratory results did not significantly differ.

Multivariate analysis showed that factors differentiating between vitamin D inadequacy and vitamin D sufficiency were higher BMI (23 kg/m2 or more) [adjusted odd ratio (AOR)= 4.67, 95% CI=1.24-17.63] and history of frequent falls (AOR=3.96, 95% CI=1.38-11.33), respectively. When analyzing the vitamin D deficiency group against the vitamin D sufficiency group, associated risks for vitamin D deficiency were being female (AOR= 2.87, 95%CI=1.06-7.78)), BMI ≥23 kg/m2 (AOR=7.20, 95% CI=1.67-31.02), two or more falls within one year (AOR= 7.32, 95%CI=2.17-24.69) and PTH levels more than 65 pg/mL (AOR= 3.38, 95%CI=1.17-9.74). **Table 3** shows multivariable analysis logistic regression of factors associated with vitamin D inadequacy and deficiency.

Table 3. Multivariable analysis of factors associated with Vitamin D inadequacy and vitamin D deficiency

Variable	Inadequacy vs Sufficiency			Deficiency vs Sufficiency		
	AOR	95% CI	*p*-value	AOR	95% CI	*p*-value
Age ≥ 80 years	1.45	(0.61-3.45)	0.395	1.14	(0.42-3.10)	0.800
Sex (female)	1.82	(0.78-4.24)	0.165	2.87	(1.06-7.78)	0.039*
BMI (kg/m^2)						
<18.5	1.00			1.00		
18.5-22.9	1.29	(0.50-3.34)	0.599	2.03	(0.67-6.13)	0.210
≥23	4.67	(1.24-17.63)	0.023*	7.20	(1.67-31.02)	0.008*
Fall ≥ 2 times	3.96	(1.38-11.33)	0.010*	7.32	(2.17-24.69)	0.001*
Hypertension	0.98	(0.40-2.42)	0.962	0.76	(0.27-2.14)	0.608
Diabetes	1.69	(0.70-4.11)	0.244	2.29	(0.87-6.06)	0.094
Previous fracture	0.51	(0.14-1.87)	0.311	0.45	(0.10-1.99)	0.294
Pre-injury status (without gait aids)	1.50	(0.66-3.41)	0.333	1.21	(0.48-3.07)	0.688
No Vitamin D supplement	2.23	(0.74-6.71)	0.154	2.85	(0.81-9.99)	0.101
PTH > 65 pg/mL	2.39	(0.92-6.19)	0.073	3.38	(1.17-9.74)	0.024*
Albumin < 3.4 g/dL	1.60	(0.52-4.86)	0.411	2.19	(0.65-7.43)	0.207
eGFR < 45	0.78	(0.24-2.57)	0.687	0.67	(0.19-2.39)	0.535

AOR =Adjusted odds ratio, CI = Confident Interval, BMI = body mass index, PTH = parathyroid hormone, eGFR = estimated glomerular filtration rate

*p < 0.05 is statistically significant.

Discussion

Vitamin D deficiency has many negative effects on bone quality including a defect in mineralization, leading to rickets and osteomalacia. It also leads to secondary hyperparathyroidism with concomitant increase in bone turnover, leading to osteoporosis. Moreover, it affects muscle strength and balances increasing the risk of fall.[11] Together with diminished bone quantity and quality, they lead to increased risk of fracture.

Our study showed a mean level of serum 25(OH)D of 19.64 ± 10.55 ng/mL among Thai elderly patients with fragility hip fractures. The result was similar to a related study among patients with osteoporotic hip fractures at Siriraj Hospital, Thailand[7] and in Singapore.[8] As expected, among these elderly patients, serum 25(OH)D level was much lower than an average level of 30.08 ng/mL among general Thai premenopausal women reported in 2009 [12] and 31.80 ng/mL among Thai adults with an average age of 40.3 years.[13] Considering the prevalence of vitamin D inadequacy, our study reported the prevalence of 86.05%, which was slightly higher than that of the study among patients with osteoporotic hip fracture at Siriraj Hospital, Thailand which was 78.4%. [7] Predictably, the figures were obviously higher than in a normal Thai population in which the rate of vitamin D inadequacy was found to be 50.9%. [13]

Aging has been proposed to affect vitamin D metabolism in many ways, magnifying the effect of vitamin D inadequacy among the elderly.[14] Aging skin has a lower concentration of 7-dehydrocholesterol, resulting in less conversion to inactive vitamin D3. Renal function also decreases with age, hindering the capability of the kidney to synthesize 25-hydroxylase required in the final step of vitamin D activation. The elderly are also at higher risk of being housebound and exposed to less sunlight. However, comparing among elderly themselves, age at 80 or above is not a predictor of vitamin D inadequacy.

In this study, the proportion of vitamin D inadequacy was about the same among women (88.09%) and men (80.0%). On the other hand, a related study among Thai healthy adults showed that vitamin D inadequacy was 3.1-fold more frequent among women than among men.[15] The prevalence of vitamin D inadequacy was only 13.9% among men, which was far lower than that of our study, indicating that patients with hip fractures were at higher risk of hypovitaminosis D, especially among men. However, the study was conducted among healthy adults with a mean age about 40 years old whose vitamin D metabolism would differ from the elderly.

The results of this study showed that BMI of 23 kg/m2 or more was associated with vitamin D inadequacy and deficiency. This relationship was consistent with another study which showed a significantly higher BMI in a vitamin D deficiency group, compared with vitamin D insufficiency and vitamin D sufficient groups. [16] Obesity-associated vitamin D insufficiency is likely to be related to decreased bioavailability of cholecalciferol synthesized from subcutaneous tissue when exposed to ultraviolet light, and ergocalciferol or cholecalciferol from dietary sources because of increased vitamin D deposition in body fat compartment. [17]

Loss of muscle strength affects functional ability and mobility putting an elderly individual at increased risk of falls and fractures. [18, 19] Vitamin D has direct impact on muscle strength by acting on vitamin D receptors present on muscle cells which becomes fewer with aging. [20] Hypovitaminosis D may sometimes present myopathy, which can be reversed with prescription of vitamin D.[21] A meta-analysis of eight randomized controlled trials recommended an optimal serum 25(OH)D level of 24 mg/mL (60 nmol/L) to achieve 23% reduced falls.[22] Similarly, supplemental high dose vitamin D could reduce all by 19%. Correspondingly, in our finding, patients with vitamin D inadequacy and vitamin D deficiency experienced more frequent falls than individuals with optimal vitamin D status.

Production of active vitamin D is under a tight control by serum calcium, phosphate and PTH. A decrease in serum 25(OH)D leads to a minute decrease in serum calcium.[6, 23] This in turns trigger a release of PTH, referred to as, "secondary

hyperparathyroidism" and a normalization of calcium level. As expected, the mean PTH level was higher in vitamin D deficiency compared with vitamin D sufficiency groups (72.35 ± 47.46 vs. 48.94 ± 30.31 pg/mL, p=0.005). However, serum calcium level was normal in all groups of participants.

Suboptimal vitamin D status is commonly observed among elderly people as the result of various risk factors and interacting physiologic changes in this population.[14] However, this condition is treatable and also preventable. Vitamin D and calcium supplementation in osteoporotic patients is also decidedly reasonable and cost-effective from an economic point of view.[24] Therefore, we highly recommend evaluating vitamin D level among patients with fragility hip fracture and supplementing with vitamin D according to their vitamin D status, especially among patients with risk factors of vitamin D inadequacy and deficiency.

This constitutes the first study to evaluate the risk factors of hypovitaminosis D among Thai patients with fragility hip fractures. Moreover, our study also showed a high prevalence of vitamin D inadequacy among Thai elderly men raising awareness of assessing vitamin D level and optimization not only among women but also men. However, several limitations were addressed in this study. First, the study constituted a cross-sectional design which could not directly explain causation. Secondly, the study was conducted at a single institution with limited representation as nationwide data. Furthermore, not all risk factors were included in the study, i.e., daily dietary consumption of calcium and vitamin D, exposure to sunlight, and dose of previous over-the-counter vitamin D supplementation due to inability to accurately assess such information and potential risk of confounders.

Conclusion

The majority of elderly patients with fragility hip fractures had suboptimal vitamin D status. Risk factors of vitamin D inadequacy included BMI >23 kg/m2, and two or more episodes of falls. Being female and high PTH levels were also associated with vitamin D deficiency. Serum 25(OH)D assessment as well as vitamin D supplement was recommended in this patient group, especially among those with risk factors including being female, presenting obesity, high risk for fallings and elevated PTH levels.

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Disclosure

No benefits in any form have been received or will be received from a commercial party related directly or indirectly to the subject of this article.

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