Hypovitaminosis D in Long-Stay Hospitalized Patients in Songklanagarind Hospital

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Abstract

The major source of vitamin D is endogenous synthesis under sunlight exposure, thus, vitamin D deficiency is uncommon in healthy people living in a tropical area where sunshine is plentiful. However, long-stay hospitalized patients who do not get direct sunlight may become vitamin D deficient. The authors studied the prevalence of vitamin D deficiency in patients without other risk factors for vitamin D deficiency who had been admitted to Songklanagarind Hospital for longer than 27 days. The second objective was to identify predictive factors for vitamin D deficiency. Considered variables were clinical character, basic laboratory results, and intact parathyroid hormone level (iPTH). Among 60 patients studied, there were 12 patients who were vitamin D deficient and only one had a level lower than 8 ng/ml. Despite vitamin D deficiency, average serum calcium was normal. Patients in the vitamin D deficient group had lower serum corrected calcium and higher iPTH level than patients in the vitamin D sufficient group. No other clinical or laboratory data could predict a vitamin D deficiency state. In summary, the present tropical area study showed that 20 per cent of long-stay hospitalized patients who had a mild degree of vitamin D deficiency and 1.7 per cent had severe vitamin D deficit. Vitamin D supplementation is unnecessary in this group of patients.

Key word : Vitamin D Deficiency, Hospitalized Patients

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Vitamin D is essential for calcium metabolism and musculoskeletal and cellular functions. Vitamin D deficiency causes osteomalacia, secondary hyperparathyroidism[1-3], irreversible bone loss[4-7], myopathy[8,9], and increases the risk of fracture [10]. Vitamin D deficiency has a wide range of clinical manifestations. It can present with rickets or osteomalacia, the most severe chronic form of vitamin D deficiency, tetany, or bone loss and fracture, which are much more common and usually unrecognized.

The major source of vitamin D is endogenous production caused by sunlight (ultraviolet B, UVB) exposure[11]. People deprived of sunlight, such as extremely old or institutionalized persons, have a high prevalence of vitamin D deficiency[12-14]. There are also reports indicating similar findings in people unexposed to UVB no matter their age, status or geographic distribution[15-19].

Thailand is located in the tropical zone and adequate sunlight exposure is expected all year round, thus vitamin D insufficiency is not supposed to be a problem among healthy Thai people despite very low level of vitamin D supplementation in food, milk or pills. This was confirmed by Chailurkit L et al, who studied the vitamin D level in healthy Thai volunteers living in Bangkok. None had vitamin D deficiency [20]. Outdoor UVB intensity in Thailand is on average 0.67 mW/cm^2 all year long[21], and this level is adequate for vitamin D synthesis even for people who are exposed to such intensity for only a short period of time.

Sources of UVB are from sunlight, fluorescent light, or UVB light bulbs but UVB can not penetrate plastic, glass or clothing even if they are transparent or translucent[11,22]. The authors measured UVB intensity at 10 a.m., 12 a.m. and 2 p.m. in the hospital wards and compared it to the average UVB intensity outdoors. The outdoors UVB intensity was 60 times higher than in the ward (0.67 mW/cm^2 *vs* 0.01-0.02 mW/cm^2). It is possible that long-stay, hospitalized, bed-ridden patients may be vitamin D deficient. There is no information concerning vitamin D deficiency in hospitalized tropical patients. The objectives of the present study were to identify the prevalence of vitamin D deficiency in patients admitted to the hospital for longer than 27 days with no other risk factors for vitamin D deficiency, and to identify parameters predicting a vitamin D deficiency state.

MATERIAL AND METHOD

This was a cross-sectional study done in Songklanagarind Hospital, Songkhla, Thailand (lat 6°N). Inclusion criteria for studied patients were age over 15 years, admitted longer than 4 weeks, immobilization and informed consent obtained. Exclusion criteria for this study consisted of patients who were in a terminal stage of malignancy, had AIDS, renal failure (defined as a serum creatinine concentration >1.5 mg/dl), nephrotic syndrome, liver disease (defined as a serum bilirubin concentration >2 mg/dl or clinical diagnosis of cirrhosis), malabsorption or taking drugs that might affect vitamin D metabolism (anticonvulsants, rifampicin, glucocorticoid, therapeutic vitamin D) or direct exposure to a UVB lamp, as well as reports of direct sun-light exposure after interview with nurses or patient. One hundred and four consecutive adult patients admitted for longer than 4 weeks were recruited. Forty four patients were excluded, mostly from renal failure or taking drugs interfering with vitamin D metabolism, leaving 60 patients in the study. The data collected included age, sex, duration of hospital stay, body mass index [BMI, as weight (kg) / height^2 (m^2)], and disease causing hospitalization. Fasting blood and spot urine samples were obtained. Serum calcium, phosphorus, alkaline phosphatase, albumin, urine calcium, and creatinine were measured by an automated analyzer (HITACHI 917, ROCHE DIAGNOSTIC). Serum parathyroid hormone (iPTH) was measured by immunoradiometric assay (CIS bio international ORIS Group, Cedex, France); coefficients of variation were 2.1 per cent. Serum 25-hydroxyvitamin D (25 (OH) D) was measured by ^{125}I Radioimmunoassay Assay (DiaSorin® Stillwater, Minnesota USA); coefficients of variation were 10.5 per cent.

Statistical analysis

The definition of vitamin D deficiency was determined at level of serum 25 (OH) D lower than 16 ng/ml (40 nmol/L)[15,23,24].

Data were expressed as mean (± SD) or median (ranges) for parametric data or nonparametric data respectively. Correlation between parameters was evaluated by Spearman rank or Pearson correlation coefficient. Comparison between vitamin D deficient patients and vitamin D sufficient patients was made by unpaired *t*-test or Mann-Whitney U test when appropriate. P-value<0.05 was considered statistically significant.

Ethical consideration

The study was approved by the Ethical Committee of Songklanagarind Hospital, and oral consent was obtained from the patients.

RESULTS

The characteristics of patients are shown in Table 1. Mean age was 50.7 years old, ranging from 15 to 94 years old. There were 27 female patients and 33 male patients. Seven patients were taking multivitamins with vitamin D content 300 IU/tablet. This group of patients was thin with a mean BMI of 19.96 kg/m^2. Median duration of hospitalization was 42.7 days. Hematologic patients often had longer duration of hospitalization. Nearly half of the long-stay hospitalization patients were patients with a haematologic malignancy who needed a prolonged coarse of chemotherapy and antibiotics. Ten studied patients were patients with chronic obstructive pulmonary disease admitted with respiratory tract infection requiring ventilatory support, 7 were orthopaedic patients who were admitted for fracture of a long-bone or cord injury, and 8 were patients suffering from cerebrovascular diseases. All of them were immobilized.

Laboratory data are shown in Table 2. Average serum albumin was 3.1 g per cent and 93 per cent of patients were hypoalbuminemia (serum albumin <4 g%). Because of the high prevalence of low serum albumin, the authors analyzed serum calcium adjusted for serum albumin by formula; corrected serum calcium = measured serum calcium + [0.8*(4-measured serum albumin)]. This group of patients had normal serum calcium levels as well as serum phosphorus. Only 2 had hypocalcemia. Urinary calcium excretion was high in this group of patients. Forty per cent of patients had a normal urinary calcium-creatinine ratio (50-250 mg calcium/g creatinine), whereas 43 per cent of them had hypercalciuria (data not shown). Despite hypocalcemia in 2 patients, only one patient had hyperparathyroidism. There was a wide range of serum alkaline phosphatase levels with nonparametric distribution.

Among the clinical characteristics, there were associations between age and serum albumin (r=-0.49, p=0.002), duration of hospital stay and BMI (r=-0.38, p=0.016), corrected serum calcium and phosphorus (r=0.44, p=0.005), and corrected serum calcium and serum iPTH (r=-0.44, p=0.004).

Table 1. Clinical characteristics of 60 patients.

Parameters	Mean ± SD	
Age (years)	50.7 ± 23.1	
Sex (M : F)	33 : 27	
Diagnosis		%
Malignancy	26	43.3
Respiratory	10	16.7
Orthopedic	7	11.7
Stroke	8	13.3
Other	9	15
Length of stay (days)	42.7 (28-82)	
BMI (kg/m^2)	19.96 ± 3.34	

The distribution of 25 (OH) D concentrations is shown in Fig. 1. It is normally distributed with an average value of 21.86 ng/ml (range 7.01-43.24). Twelve patients had vitamin D deficiency. Only one had a level of 25 (OH) vitamin D less than 8 ng/ml. There was no correlation between vitamin D level and corrected serum calcium or other clinical parameters. However, there was significant correlation between serum 25 (OH) D level and iPTH (r= -0.325, p=0.016) as shown in Fig. 2.

A comparison of interesting variables between the vitamin D deficiency and vitamin D sufficiency groups is shown in Table 3. Clinical characters included age, sex, diseases leading to admission, duration of hospital stay, and nutritional status (represented by BMI or serum albumin). Serum phosphorus and serum alkaline phosphatase were not different between both groups. Serum corrected calcium was higher in the vitamin D sufficient group and serum iPTH was lower in the vitamin D sufficient group. Urinary calcium/creatinine levels were not different

Table 2. Baseline laboratory data.

Parameters	Mean ± SD	Ranges
Alkaline phosphatase (IU/L)	180.7 ± 219	44 - 1,482
Albumin (g/dl)	3.1 ± 0.5	1.7 - 4.2
Phosphorus (mg/dl)	3.8 ± 0.7	1.8 - 5.3
Corrected calcium (mg/dl)	9.4 ± 0.6	7.04 - 11.28
iPTH (pg/dl)	21.2 ± 16.9	0.35 - 88.2
Urine calcium creatinine ratio (mg/g Creatinine)	238 ± 196	68 - 842

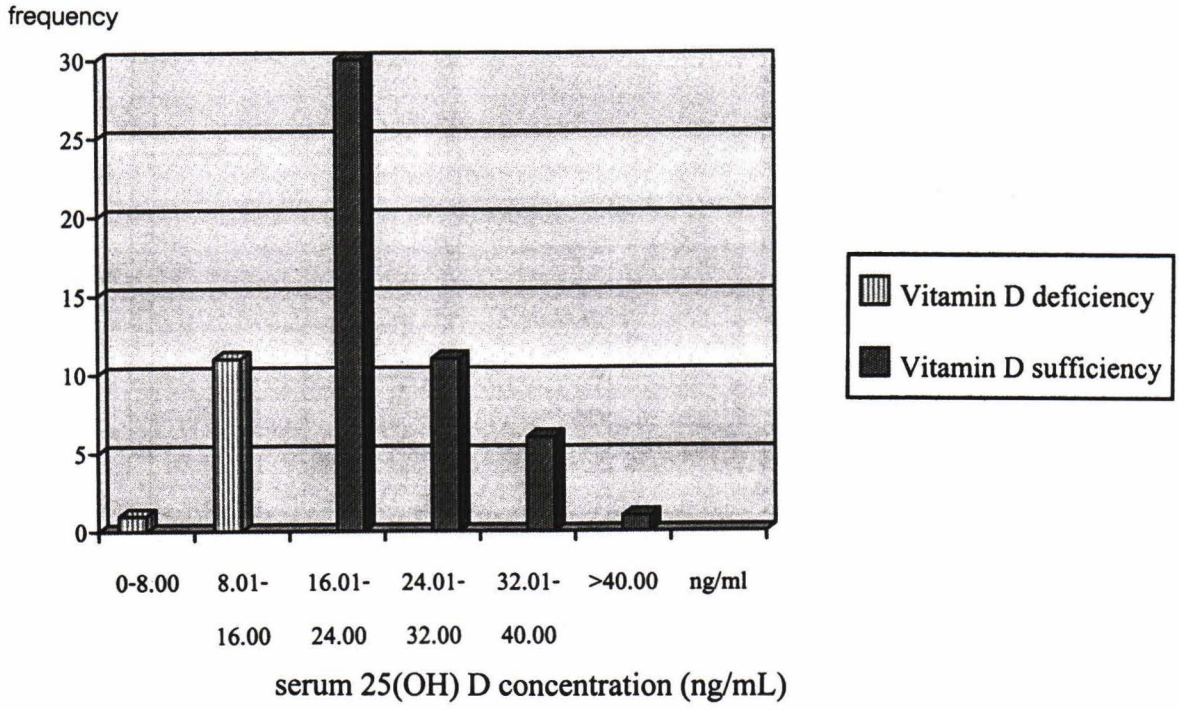

Fig. 1. Frequency distribution of 25 (OH) D concentrations.

Table 3. Comparison of clinical and laboratory values between vitamin D sufficient and vitamin D deficient groups.

Variables	Vitamin D sufficient N=48	Vitamin D deficient N=12
Age (years)	52.5 (15-94)	40 (16-96)
Hospital stay (days)	40 (28-81)	34.5 (28-83)
Albumin (g/dl)	2.9 ± 0.5	3.1 ± 0.5
Phosphorus (mg/dl)	3.8 ± 0.7	3.7 ± 0.5
Calcium (mg/dl)	9.45 (7.0-11.3)	9.1* (7.6-10.4)
Alkaline phosphatase (IU/L)	111 (59-232)	135.5 (44-1,482)
Urine calcium creatinine ratio (mg/g Cr)	211.2 (13.1-842)	174.3 (6.8-750)
iPTH (pg/ml)	25 (0-53.3)	35* (5.2-88.8)

* = $p < 0.05$

in both groups. Neither average serum calcium nor average iPTH was out of normal range. There was no level of iPTH or serum calcium that could predict a vitamin D deficient state (Fig. 2). Even among patients with hypocalcemia, their serum vitamin D levels were normal.

Among 7 patients taking multivitamin supplementation, the vitamin D level was not significantly different from the rest (23.82 ± 10.8 *vs* 21.60 ± 6.69 ng/ml, respectively).

DISCUSSION

In healthy Thais, there is no vitamin D deficiency despite no vitamin D fortified milk as well as very low milk and dairy-product intake in the traditional Thai diet. Thus, it is generally believed that Thai people get vitamin D from endogenous vitamin D production after sunlight exposure. The presented patients had a surprisingly low prevalence of vitamin D deficiency. However, the average serum 25 (OH) D concentrations in the present study was

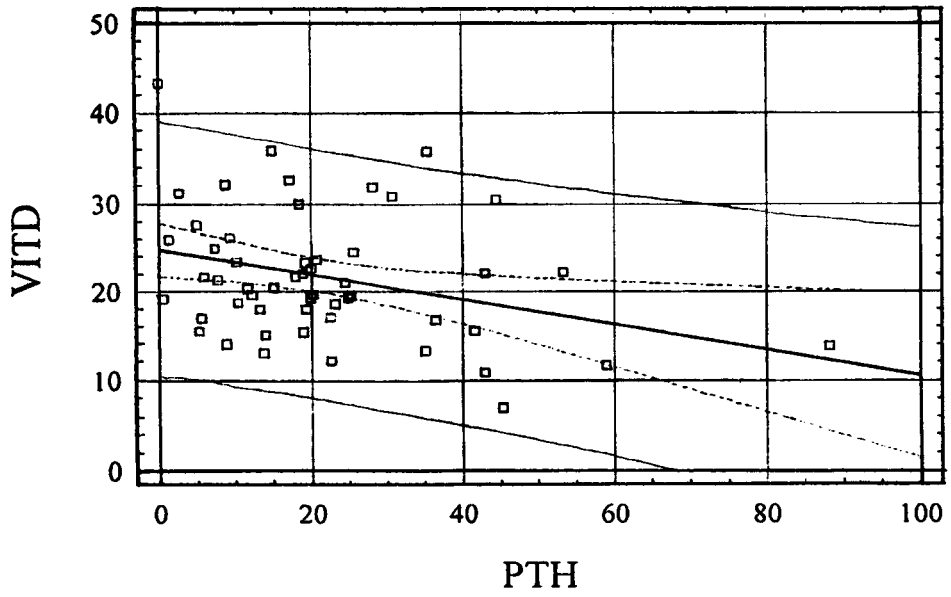

Fig. 2. Correlation between serum 25 (OH) D and serum iPTH.

much lower than that of healthy volunteers (21.8 *vs* 46 ng/ml respectively)[20]. The patients had normal iPTH levels as well as normal serum calcium levels, which was not surprising because our patients were immobilized (ventilator-bound), had a fracture of a long-bone, or were too sick to move. This finding is in contrast to that of Soontrapa S et al from Khon Kaen who found that old women in their community with low-normal vitamin D levels had higher iPTH [25]. However, the nature of the studied populations is different. The presented patients were sick and immobilized, whereas the patients in the other study were ambulatory and well. Immobilization directly stimulates bone resorption and increases the risk of hypercalcemia, thus these subjects had a normal serum calcium level, which in turn controls the iPTH level, which was also shown by the high urinary calcium/creatinine value. The presented patients had mild vitamin D deficiency, together with being immobilized, therefore serum calcium was not affected. On the other hand, such a degree of immobilization confirmed that these patients could not have sun-bathed by themselves.

The prevalence of vitamin D deficiency in this study was only 20 per cent. This could be from a very stringent selection that excluded high risk patients. However, when compared to other studies which had a similar low risk group, this was still lower. Thomas et al reported a prevalence of vitamin D deficiency of 42 per cent among low risk Boston patients newly admitted to the hospital[15]. The possibilities that there was a low prevalence of vitamin D deficiency in the presented patients are; first, there was unrecorded sun exposure. In the studied wards, UVB intensity was measured and found to be very low but in the corridor the UVB intensity was very high. In the hospital, there is a regular ward cleaning day once a month. On that day all beds as well the patients in those beds must be moved out of the inner area to the corridor for at least 1 hour during that cleaning period. It is possible that even a short period of sun exposure could maintain vitamin D status in most patients. The authors did not record the cleaning date, thus, the association between such an event and patients' vitamin D levels could not be analyzed.

Second, for the dietary vitamin D content, there was a report from Japan that peri- and postmenopausal women had a good vitamin D status despite very low UVB exposure[26]. They found that women who consumed more fish and eggs had a

higher vitamin D level. The presented patients had low serum albumin levels and it is a regular practice in the institute that patients with hypoalbuminemia will receive high protein diet, mostly from eggs. In addition, there may be other potential vitamin D containing foods such as special fish paste made from fermented salted fish viscera (Kang Tai Pla), and fermented salted fish (Budu). We did not prospectively monitor the diet, both hospital-provided and self-administered, thus, it is not possible to figure what diet may have protected the patients from a vitamin D deficiency state.

Vitamin D is responsible for maintaining normal serum calcium, and when vitamin D deficiency leads to hyperparathyroidism, that increases bone resorption as reflected by increased serum alkaline phosphatase. There were some studies(12,14,18) which supported the association of vitamin D deficiency with high serum alkaline phosphatase, but this association was not shown in the present study. There were wide ranges of serum alkaline phosphatase in the studied group even excluding patients with jaundice and clinically diagnosed cirrhosis. The authors measured total alkaline phosphatase activity which could be from liver, bone, placenta or intestine. Such high levels of alkaline phosphatase could be from liver diseases such as fatty liver, infiltrative liver diseases, congestion of the liver or even nonspecific elevation from infection or drugs.

Limitation of study

The present study was a cross-sectional study, thus it is uncertain whether long-stay was the cause of vitamin D deficiency, and it is possible that some patients may have been vitamin D deficient before admission. The authors did not measure serum magnesium, thus it is still obscure why the hypocalcemic patient did not have secondary hyperparathyroidism, as well as the quite normal serum parathyroid levels in the whole group. Third, serum calcium with albumin was adjusted which may not represent ionized calcium, thus, serum ionized calcium might be lower in the vitamin D deficiency group. However, there is very limited use of ionized calcium in many hospitals and laboratories and the authors wanted to use a generally available laboratory method to predict hypovitaminosis D, thus we chose a simple technique in measuring serum calcium was chosen.

SUMMARY

20 per cent vitamin D deficiency in low risk, long-stay hospitalized patients but was found only one patient had severe vitamin deficiency (25 (OH) D <8 ng/mL). There was no clinical or laboratory data that could predict vitamin D deficiency. Immobilized patients had high urinary calcium excretion so routinely prescribed vitamin D could increase urinary calcium excretion and may precipitate stone formation. The authors do not recommend prescribing vitamin D supplementation to all patients. This data can not be extrapolated to high risk patients for vitamin D deficiency. Further studies are needed to explore the effect of prolonged hospitalization, as well as, dietary assessment of vitamin D and calcium.

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ภาวะพร่องวิตามินดีในผู้ป่วยที่นอนโรงพยาบาลเป็นเวลานานในโรงพยาบาลสงขลา-นครินทร์

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แหล่งใหญ่ของวิตามินดีในคนคือการสังเคราะห์วิตามินดีโดยอาศัยรังสีอัลตร้าไวโอเลต บี จากแสงแดด ดังนั้นจึงพบภาวะพร่องวิตามินดีได้น้อยในผู้มีสุขภาพดีในเขตร้อน อย่างไรก็ตามในผู้ป่วยที่นอนโรงพยาบาลเป็นเวลานานและไม่ได้รับแสงแดดก็อาจจะมีภาวะพร่องวิตามินดี การศึกษานี้เพื่อหาความชุกของภาวะพร่องวิตามินดีในผู้ป่วยที่นอนโรงพยาบาลเป็นเวลานานเกิน 27 วัน โดยไม่มีปัจจัยเสี่ยงต่อภาวะพร่องวิตามินดีและเพื่อหาปัจจัยที่สามารถทำนายภาวะพร่องวิตามินดี ตัวแปรที่ศึกษาประกอบด้วยลักษณะทางคลินิก การสืบค้นพื้นฐาน และระดับพาราธัยรอยด์ฮอร์โมน ในเลือด ผู้ป่วยจำนวน 60 ราย มี 12 รายที่พบภาวะพร่องวิตามินดี (ร้อยละ 20) และมีเพียง 1 ราย ที่มีภาวะขาดวิตามินดีอย่างรุนแรง (ระดับ 25 (OH) D ต่ำกว่า 8 ng/ml) กลุ่มที่มีภาวะพร่องวิตามินดีมี iPTH สูงกว่า และระดับ corrected calcium ต่ำกว่ากลุ่มที่ไม่มีภาวะพร่องวิตามินดี (ระดับ iPTH และ corrected calcium = 32.89 $\pm$ 15.38 pg/ml และ 9.26 $\pm$ 0.45 mg/dl (p=0.048) และ 21.51 $\pm$ 8.23 pg/ml และ 9.48 $\pm$ 0.16mg/dl (p=0.038) ในกลุ่มที่มีภาวะพร่องวิตามินดี และกลุ่มที่ไม่มีภาวะพร่องวิตามินดี ตามลำดับ) โดยที่ไม่มีความแตกต่างระหว่างปัจจัยอื่นที่สนใจ อย่างไรก็ตามระดับ iPTH และ corrected calcium ไม่สามารถทำนายภาวะพร่องวิตามินดีได้

โดยสรุป ผู้ป่วยที่นอนในโรงพยาบาลสงขลานครินทร์นานและไม่ได้รับแสงแดดโดยตรง มีความชุกของภาวะพร่องวิตามินดีร้อยละ 20 แต่มีเพียง ร้อยละ 1.7 ที่มีภาวะขาดวิตามินดีรุนแรงและไม่มีผลต่อระดับแคลเซียมในเลือด จึงไม่จำเป็นต้องให้วิตามินดีเสริมในทุกราย

คำสำคัญ : ภาวะพร่องวิตามินดี, ผู้ป่วยที่นอนโรงพยาบาลเป็นเวลานาน

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