

A case of vitamin D deficiency masquerading as occult malignancy

Mohammed Ahmed,* Haroon A Faraz,† Abdulraof Almahfouz,* Abdullah Alarifi,* Hussein Raef,*
Fouad Al-Dayel,‡ Abdulaziz Al-Sugair,§ Ali Alzahrani*

At present, the diagnosis of a “brown tumor” is a clinical curiosity. It is considered to be a complication of severe and rapidly progressive hyperparathyroidism (HPT). Indeed, such a presentation is typical of a patient harboring a parathyroid carcinoma. The incidence of brown tumors is 3% in the benign form of primary hyperparathyroidism.¹ In secondary HPT, the incidence of brown tumors is under 2% and is caused by chronic renal failure.¹ Brown tumors are locally destructive lesions consisting of fluid-filled cysts that are rich in highly vascularized fibrous tissue containing hemorrhagic spots. Blood pigment (hemosiderin) will accumulate, which imparts a reddish-brown hue and hence the name “brown tumor”.¹ Brown tumors are demonstrated radiologically as lesions of osteitis fibrosa cystica.¹

We describe a young lady who was erroneously diagnosed elsewhere as a case of metastatic bone disease. Our evaluation documented this as a case of vitamin D deficiency (VDD) causing secondary hyperparathyroidism (SHPT) with diffuse distribution of brown tumors in her skeleton. Following vitamin D and calcium treatment, the patient improved.

Case

A 17-year old single woman had mandibulectomy twice at two different outside hospitals for a left mandibular mass 16 months prior to presentation. She was left with a foul smelling, disfiguring, draining sinus. Evaluation at the outside hospital showed diffuse skeletal “lytic lesions” resulting in a diagnosis of metastatic giant cell tumor vs skeletal metastatic disease of unknown primary source. This diagnosis had caused an emotional strain on the patient and the family. She was then referred to the radiation oncology department at King Faisal Specialist Hospital where she received 400 rads to the mandible, followed by chemotherapy and endocrine consultations. She gave a history of bilateral hip pain.

Laboratory results were as follows: serum calcium 2.12 mmol/L (reference range, 2.1-2.6), albumin 44 g/L (36-48), phosphate 0.87 mmol/L (0.90-1.5), alkaline phosphatase 529 U/L (30-135), parathyroid hormone (PTH) (intact) 989 ng/L (10-65), vitamin 25-hydroxy (OH) D3 11 nmol/L (25-116), creatinine 65 µmol/L (40-90), creatinine clearance 1.7 mL/s (1.3-2.1), and 24-h urine calcium 0.91 mmol (2.5-6.3). A work-up for celiac disease as a cause of malabsorption was negative. X-rays showed an absence of a major part of the ramus left mandible that was replaced by a metallic prosthesis at an outside hospital (Figure 1). Chest x-rays showed an osteolytic lesion in the right eighth rib, and marked osteopenia of the dorsal spine. X-ray of the pelvis showed marked osteopenia, and a 5 x 2-cm osteolytic lesion in the right acetabulum and pathological fracture of the superior and in-

*From the *Department of Medicine, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia, †Wayne State University, Detroit Medical Center, USA, ‡Pathology and Laboratory Medicine, §Radiology, King Faisal Specialist Hospital & Research Centre, Riyadh, Saudi Arabia*

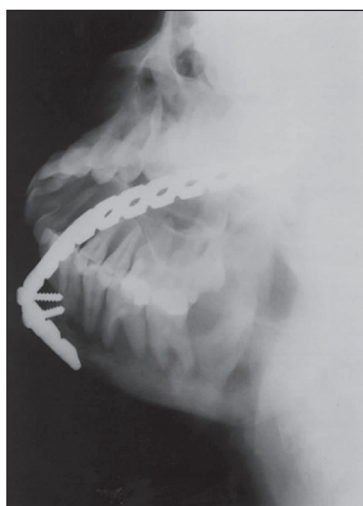
Correspondence and reprint requests:

*Mohammed Ahmed, MD
Department of Medicine, MBC 46
King Faisal Specialist Hospital & Research Centre
P.O. Box 3354
Riyadh 11211
Saudi Arabia
mohammedahmed88@hotmail.com*

*Accepted for publication
August 2005*

Ann Saudi Med 2006;26(3):231-236

Figure 1 X-ray of left mandible showing a resected left mandible ramus that is replaced by a metallic device.



ferior pubic rami in addition to a 4 x 2 cm osteolytic in the left iliac wing (Figure 2A). Hand x-rays (not shown) showed subperiosteal bone resorption of several middle phalanges. A whole body bone scan (Figure 3A) showed multiple “hot spots” in the skull, pelvic bones, multiple ribs, left hip, femur, tibia, and sternum. BMD measurement of the lumbar spine was 0.6 g/cm² (50% of adult control); T and Z scores were -6 standard deviations each. Our review of slides of specimens taken at another hospital showed a multinucleated giant-cell lesion and spindle cells dispersed within the loose stroma with increased vascularity. The spindle cells showed monomorphic nuclei without mitosis (Figure 4). Evaluation for celiac disease was negative (negative serological workup for anti-tissue glutaminase, anti-endomysium [IgA] antibodies, anti-reticulin [IgA] antibodies, anti-gliadin [IgA and IgG] antibodies). Our diagnosis was vitamin D deficiency related to secondary hyperparathyroidism. The patient was treated with calcium supplements 3.6 grams daily and calcitriol 1µg daily and showed considerable improvement.

A follow-up BMD at 5 months showed osteoporosis albeit with some improvement in lumbar spine BMD to 0.871 g/cm² (T and Z scores of -3.3 SD each) and a femoral neck BMD of 0.72 g/cm², or 72% of control (T/Z score: -2.3/1.8 SD, respectively). A BMD at the 17-month follow up showed further improvement in the lumbar spine BMD to 0.951 g/cm² (T score of -2.1 SD [79%] and Z score of -1.2 SD [87%]). For the whole body BMD was 1.027 g/cm² (T score of -1.2 SD [91%] and the Z score was zero SD [100%]). Serial serum calcium determinations were normal (2.31-2.55 mmol/L), and

PTH declined dramatically to 190 ng/L a month posttreatment, normalized to 45 ng/L at 3 months, declined to 15 ng/L at 5 months post-treatment and remained normal thereafter (Figure 5). The decline in serum alkaline phosphatase lagged behind that of the PTH, dropping to a normal value at 5 months posttreatment and remained normal thereafter (Figure 5). There was a substantial improvement in the skeletal x-rays (Figure 2B) and bone-scan findings (Figure 3B) over a 14-month follow-up. At follow-up the patient underwent removal of the mandibular metallic plate and closure of the fistula; this was followed up by reconstructive surgery using a hip graft with Wurzburg miniplates. The patient had been followed up for 30 months as of this writing and was enjoying good health. At her last follow-up the following tests were all within normal limits: serum calcium 2.52 mmol/L, phosphate 1.2 mmol/L, alkaline phosphatase 127 U/L, albumin 40 g/L, creatinine 64 µmol/L, vitamin 25-OH D3 27 nmol/L, and PTH 23 ng/L.

Discussion

The patient described here had severe VDD, very high serum PTH, and alkaline phosphatase, hypocalciuria, osteitis fibrosa cystica, osteoporosis, and histological findings of brown tumor with normal kidney function tests, and no evidence of malabsorption such as celiac disease. These data confirm unequivocally the diagnosis of VDD-related secondary hyperparathyroidism (SHPT). Brown tumors as a complication of VDD-associated SHPT, as documented here, are most unusual.

VDD is a common problem in the population in Saudi Arabia, including young and otherwise healthy persons.² It is rather curious that with an abundance of sunlight, very low levels of serum 25-OH D3 were observed in people in Saudi Arabia.² VDD in Saudi Arabia is possibly related to inadequate sun exposure based on the social dressing customs and the dietary habit of eating high wheat fiber containing lignin, which binds to bile acids interfering with vitamin D absorption. However, Sedrani reported low levels of vitamin D in Saudis and non-Saudis, including people with white and dark skin colors, thereby excluding the possibility of skin pigmentation and the traditional clothing style as contributing factors.² Other factors such as racial differences in vitamin D metabolism have not been studied in the Saudis.

Vitamin D has a pivotal role in mineral homeostasis and bone metabolism. Vitamin D3, or cholecalciferol, is synthesized in the skin. Its precursor, 7-

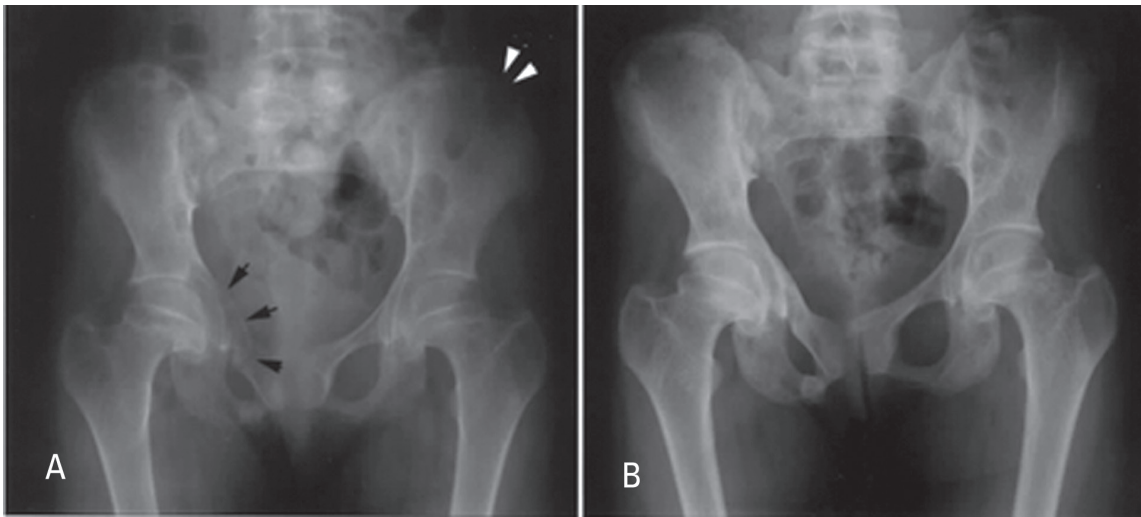


Figure 2. A) X-ray of the pelvis showing marked osteopenia. A 5 x 2 cm large expansile osteolytic lesion is seen (black arrows) adjacent to the medial wall of the right acetabulum with an associated pathological fracture of the right superior pubic ramus (black arrowhead). A 4 x 4 cm osteolytic lesion is seen (2 white arrowheads) in the left iliac wing. B) Shows improved mineralization in the bones, resolution of the previously seen right acetabular lytic lesion, symphysis pubis, and the left iliac bone following vitamin D and calcium replacement.

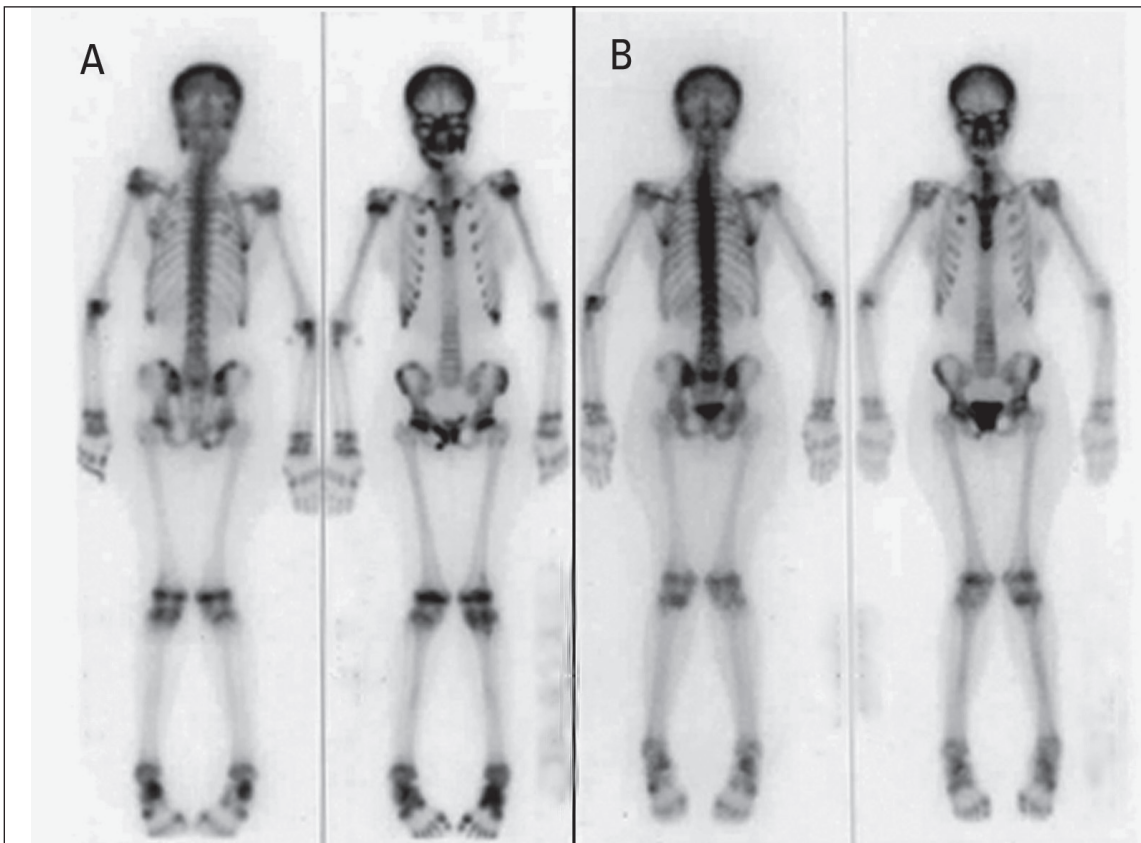


Figure 3. Whole body scan (WBS) using ^{99m}Tc methylene diphosphonate (MDP): A) shows multiple "hot spots" in the skull, ribs, right pubic ramus, around pubic symphysis, left iliac wing, left supratrochanteric area. B) Fourteen months following treatment the whole body scan demonstrates a substantial improvement in these "hot spots"; however, increased uptake is still seen in the right inferior pubic ramus, and right second rib.

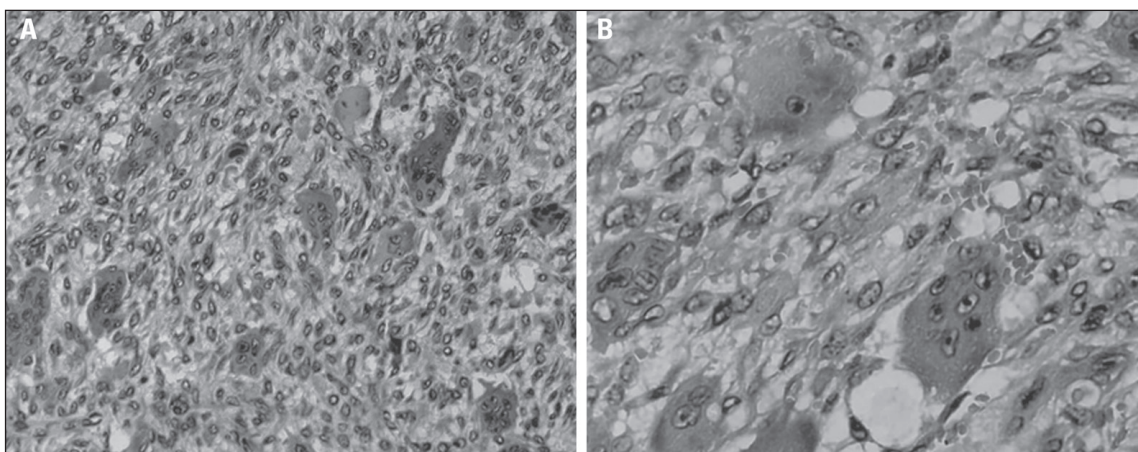


Figure 4. Histopathology of the mandibular tumor resected at the outside hospital: A) intermediate power photomicrograph showing a giant-cell rich lesion; interspersed between the giant cells and within the loose stroma are spindle cells displaying monomorphic nuclei without mitoses. B) High power photomicrograph of this brown tumor shows multinucleated giant-cells and spindle cells dispersed within the loose stroma with increased vascularity.

dehydrocholesterol, is metabolized by a narrow band of UV light (UVB 290-315 nm) from the sun into previtamin D₃, which is isomerized to vitamin D.³ A low serum 25-OH D₃ is the hallmark of VDD.³ However, there is no consensus on the precise definition of VDD based on serum 25-OH D₃ levels,⁴ and different cutoff points, ranging between 15 to 37 ng/mL (36 to 88 nmol/L), have been suggested as a minimum requirement for the diagnosis.⁴

Lips has defined and proposed a staging of VDD.³ A serum 25-OH D₃ level below 20 ng/mL (50 nmol/L) is called mild VDD; this is associated with a slight but definite increase in serum PTH concentration with a mild increase in bone turnover. When the serum 25-OH D₃ level is below 10 ng/mL (25 nmol/L), a moderate VDD is diagnosed; this is associated with a moderate increase (up to 30%) in serum PTH concentration and increased bone turnover.³ Lips defined severe VDD as a 25-OH D₃ below 5 ng/mL (12.5 nmol/L); PTH values may increase by 30% and be associated with a mineralization defect leading to overt osteomalacia.³ VDD causing SHPT results in high bone turnover, bone loss, mineralization defects, and fractures.³ Using Lips criteria, our patient had severe VDD that was associated with evidence of severe mineralization defect, resulting in diffuse skeletal cystic lesions of large giant cell lesions, a distinctly unusual presentation of VDD. Vitamin D supplementation in conjunction with calcium resulted in a dramatic regression of SHPT, and an increase in bone mineral density in our patient.

In primary hyperparathyroidism, coexisting

VDD is associated with important features of disease activity: serum PTH, alkaline phosphatase, and parathyroid weight.⁵ Adjusted serum calcium, serum PTH, alkaline phosphatase values and parathyroid gland weights were each significantly higher in a group of 51 hyperparathyroid patients with 25-OH D₃ values less than 15 ng/mL (36 nmol/L) than in a group of 97 patients with serum 25-OH D₃ values of 15 ng/mL (36 nmol/L) or higher.⁵ To our knowledge, similar data pertaining to SHPT of VDD is not available. Serum 25-OH D₃ is the best index of VD nutritional status and serum PTH is the best indicator of parathyroid hyperplastic cell mass. Our findings in this and several similar patients in our experience suggest an inverse relationship between serum vitamin D and PTH levels. We suggest that severe VDD is associated with a marked increase in parathyroid gland weight and serum PTH values with severe metabolic bone disease.

VDD is a common health problem worldwide. In the developed countries, VDD and related defects of bone mineralization resulting in hip fractures are recognized increasingly.^{3,6,7} This is also a special public health problem in the northern latitudes, among the elderly and in institutionalized patients.^{3,8,9} Paradoxically, VDD and the related clinical problems of rickets, osteomalacia, and osteoporosis are also being reported increasingly from the sunny regions of the world.¹⁰⁻¹² In India and China, VDD is endemic.^{11,12} Severe VDD (a mean±SD 25-OH D₃ value of 8.7± 5.2 ng/mL) has been reported in 20 patients from India; 90% of these had osteitis fibrosa cystica.¹² Similarly, Bilezikian et al have reported findings of

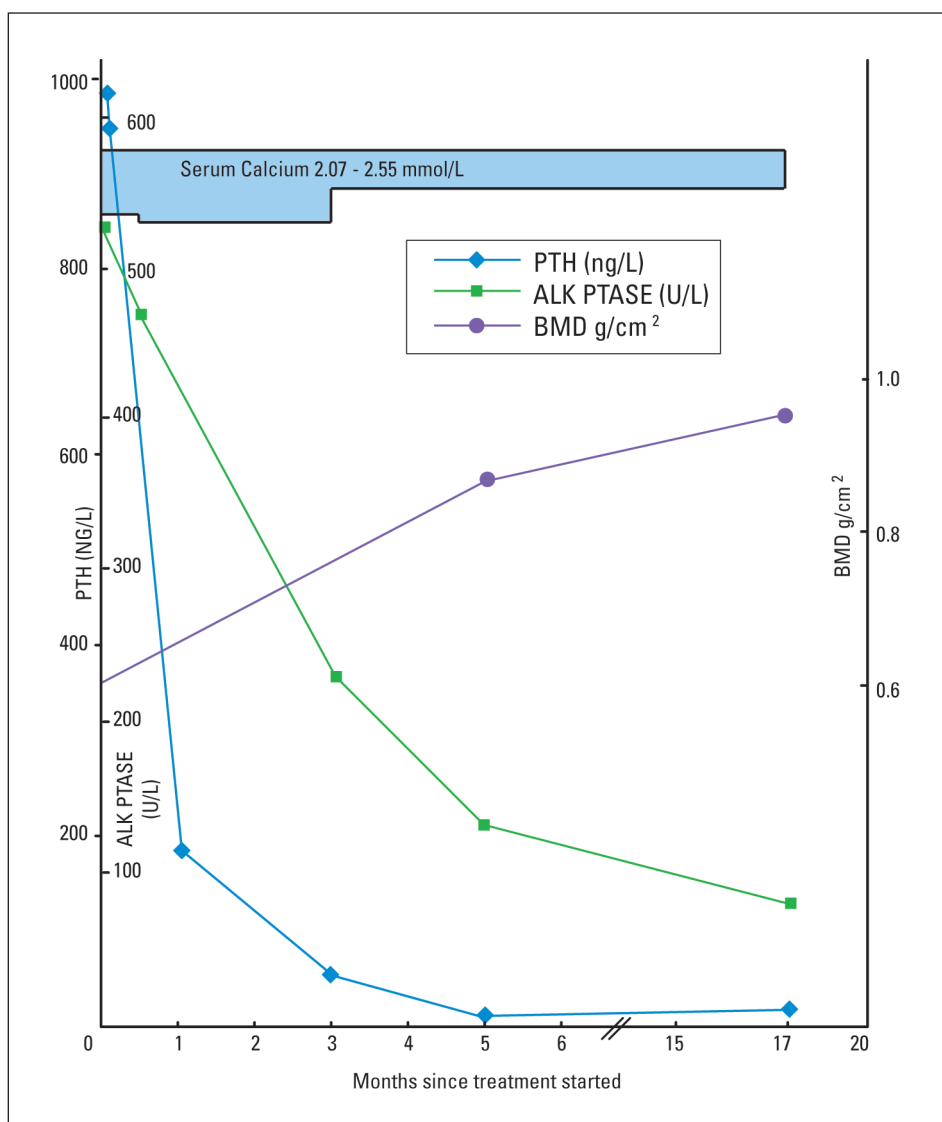


Figure 5. Resolution of vitamin D deficiency-related secondary hyperparathyroidism associated with improvement in bone mineral density findings following treatment. Note the dramatic decline of the PTH at one month post-treatment and normalization thereafter. The decline in alkaline phosphate lagged behind that of the PTH but normalized at 5 months post-treatment.

severe VDD among 134 Chinese patients who had a mean 25-OH D value of 8.8 ± 7.2 ng/mL.¹³ VDD has also been reported from the sunny areas of the Middle East and the Mediterranean.^{10,14} A recent report of 316 Lebanese, including 51 veiled women, between 30-50 years of age, described VDD.¹² Serum 25-OH D levels <12 ng/mL (<28 nmol/L) were found in 72% and <5 ng/mL (<12 nmol/L) among 62% of the veiled women.¹⁰

When confronted with multiple osteolytic lesions, it is mandatory to exclude osteitis fibrosa cystica (brown tumors) since such skeletal lesions may mimic metastatic bone disease. Our patient

had widespread brown tumors of the bone in typical sites. Atypical involvement, such as the base of the cranium in the area of the sphenoid sinus and orbit, is rare and may produce a neurological deficit as a primary clinical presentation.¹ Our case is illustrative of the vagaries encountered in the diagnosis of VDD. An understanding of the unusual aspects of vitamin D-related bone disease will help prevent mutilating and unwarranted forms of treatment.

The authors thank Prescilla Manaban-Vidonia for secretarial help in preparing the manuscript.

References

- ¹ Kanaan I, Ahmed M, Rifai A, Alwatban J. Sphenoid Sinus Brown Tumor of Secondary Hyperparathyroidism: Case Report. *Neurosurgery*, 1998; 42 (6); 1374-1377.
- ² Sedrani SH, Elidrisy AWTH, El Arabi KM. Sunlight and Vitamin D status in normal Saudi subjects. *Am J Clin Nutr*, 1983; 38; 129-132.
- ³ Lips P. Vitamin D Deficiency and Secondary Hyperparathyroidism in the Elderly: Consequences for Bone Loss and Fractures and Therapeutic Implications. *Endocrine Reviews*, 2001;22(4);447-501.
- ⁴ Bandeira F, Caldas G, Freese E, Griz L, Faria M, Baneira C. Relationship Between Serum Vitamin D status and Clinical Manifestations of Primary Hyperparathyroidism: *Endocrine Practice*, 2002; 8 (4) 266-270.
- ⁵ Rao DS, Honasoge M, Divine GW, et al. Effect of vitamin D nutrition on parathyroid adenoma weight: pathogenetic and clinical implications. *J Clin Endocrinol Metab*. 2000; 85; 1054-1058.
- ⁶ Bruce DG, St. John A, Nicklason F, Goldswain RT. Secondary hyperparathyroidism in patients from Western Australia with hip fracture: relationship to type of hip fracture, renal function, and vitamin D deficiency. *J AM Geriatr Soc*, 1999; 47; 354-359.
- ⁷ Sahota O, Masud T, San P, Hosking DJ. Vitamin D insufficiency and increases bone turnover markers and enhances bone loss at the hip in patients with established vertebral osteoporosis. *Clin Endocrinol (Oxf)*. 1999; 51; 217-221.
- ⁸ Chapuy MC, Preziosi P, Maamer M, et al. Prevalence of vitamin D insufficiency in an adult normal population. *Osteoporos Int*. 1997; 7; 439-443.
- ⁹ Lips P, Wiersinga A, Van Ginkel FC, et al. The Effect of Vitamin D supplementation on Vitamin D status and parathyroid function in elderly subjects. *J Clin Endocrinol Metab*. 1998; 67; 644-650.
- ¹⁰ Gannage-Yared MH, Chemali R, Yaacoub N, Halaby G. Hypovitaminosis D in a sunny country: relation to lifestyle and bone markers. *J Bone Miner Res*. 2000; 15; 1856-1862.
- ¹¹ Mithal A, Rao D, Meng Y. Clinical presentation of primary hyperparathyroidism: India, Brazil and China. In: Bilezikian JP, Levine MA, Marcus R, eds. *The parathyroids*. 2nd ed. San Diego, CA: Academic Press, 2001: 375-386.
- ¹² Harinarayan CV, Gupta N, Kochupillai N. Vitamin D status in primary hyperparathyroidism in India. *Clin Endocrinol (Oxf)*. 1995; 43;351-358.
- ¹³ Bilezikian JP, Meng X, Shi Y, Silverberg SJ. Primary hyperparathyroidism in women: a tale of two cities-New York and Beijing. *Int J Fertil womens Med*. 2000; 45; 158-165.
- ¹⁴ Alagol F, Shihadeh Y, Boztepe H, et al. Sunlight exposure and vitamin D deficiency in Turkish women. *J Endocrinol Invest*. 2000; 23; 173-177.