ATYPICAL PRIMARY HYPERPARATHYROIDISM DUE TO HYPOVITAMINOSIS D

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(_abstract): Vitamin D deficiency is nowadays very common in the general population and also in patients with primary hyperparathyroidism. Hypovitaminosis D may modify the clinical features and the severity of primary hyperparathyroidism. We present the case of a 75-year-old woman with a 10 year history of nephrolithiasis and severe osteoporosis, with multiple fragility fractures. Her bone and kidney status required a more thorough metabolic assessment. Despite minimal changes in serum calcium and phosphate levels, parathyroid hormone (PTH) level was markedly elevated. Ultrasound and specific Sesta-MIBI scintigraphy diagnosed and localized a left parathyroid adenoma. Vitamin D assessment showed levels in the range of hypovitaminosis. Vitamin D deficiency may mask hypercalcemia despite high serum PTH levels, and does not seem to diminish but on the contrary increases the risk of kidney lithiasis, as well as the deleterious effects of hyperparathyroidism on bone. Keywords: PRIMARY HYPERPARATHYROIDISM, VITAMIN D, PARATHYROID HORMONE.

Primary hyperparathyroidism (hPTH) is currently considered one of the most common endocrine diseases, with a prevalence reaching 1-2% among women aged over 50 (1). Excessive parathyroid hormone (PTH) secretion may be deleterious due to massive bone demineralization and severe hypercalcemia accompanied by a higher risk of kidney lithiasis and soft tissue calcification. However, the spectrum of severity of hPTH has widely changed in recent decades, especially since milder forms are diagnosed by routine calcium measurement, cervical ultrasound and bone mineral density assessed by Dual X-ray absorptiometry (DXA).

PTH and vitamin D are known to be the two major regulators of calcium and bone metabolism, the two hormones having direct interferences. PTH activates vitamin D to 1,25(OH)2D3 in the kidney by stimulating 1-alpha hydroxylase. Active intestinal calcium absorption is directly stimulated by 1,25(OH)2D3. At its turn, 1,25(OH)2D3 downregulates PTH secretion by direct effects on the parathyroid glands (2).

The increase of life span and the decrease of sunlight exposure due to modern
life caused a vitamin D deficiency epidemic in the general population. Interestingly, vitamin D deficiency was found by several authors to be more common in patients with primary hPTH than in the general population (3,4,5). The consequences of vitamin D deficiency in these patients and its appropriate management are unclear. We present the case of a 75-year-old woman diagnosed with primary hPTH and vitamin D deficiency.

**CASE REPORT**

BG, a 75-year-old woman was admitted to the Endocrinology Department of “St. Spiridon” Hospital for the metabolic investigation of severe osteoporosis with multiple pathological fractures. Our third age patient had a body weight in the lean range (BMI = 21 kg/m2), therefore the presence of osteoporosis was not a surprise. However, the patient had a profoundly decreased bone mineral density (BMD) evaluated by DXA in all locations, with the lowest T-score found at the distal 1/3 of the radius (Table I), highly suggestive of primary hPTH. Anamnesis revealed not only a 10-year history of multiple fractures, but also relapsing nephrolithiasis for which she underwent several sessions of extracorporeal shockwave lithotripsy, increasing our suspicion of primary hPTH. However, serum calcium and phosphate were only mildly out of the normal range (Table II).

<table>
<thead>
<tr>
<th>Normal ranges</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>8.8-10.2 mg/dl</td>
<td>10.78</td>
</tr>
<tr>
<td>Phosphate</td>
<td>2.5-4.7 mg/dl</td>
<td>2.25</td>
</tr>
<tr>
<td>Calciuria</td>
<td>100-300 mg/24h</td>
<td>408</td>
</tr>
<tr>
<td>PTH</td>
<td>15-65 pg/ml</td>
<td>228</td>
</tr>
<tr>
<td>25-OH-D</td>
<td>&gt;30 ng/ml</td>
<td>10.59</td>
</tr>
</tbody>
</table>

The association of “stones and bones” complications raised the suspicion of primary hPTH. In contrast with the important skeletal and kidney impact, the metabolic profile of our patient showed only mild hypercalcemia (10.78 mg/dl) and hypophosphatemia (2.25 mg/dl), albeit significant hypercalciuria (408 mg/24h). The measurement of PTH revealed an elevated level (228 pg/ml). Renal function of our patient was intact: urea 36 mg/dl (reference range 21-43 mg/dl), creatinine 0.82 mg/dl (reference range 0.57-1.11 mg/dl). The discrepancy between the mild changes in serum calcium and phosphate and the marked increase in serum PTH level made us evaluate vitamin D levels that were found decreased (10.59 ng/ml) (tab. II).

Neck ultrasound revealed a hypoechoic nodule, posterior to the left thyroid lobe, measuring 1.6x0.8cm, with peripheral vascularization (fig. 1). The specific scintigraphic investigation showed increased uptake of Technetium (Tc) 99m Sestamibi (MIBI) in the suspected nodule, localizing a left parathyroid adenoma (fig. 2).

The patient was advised to undergo a minimally invasive approach to remove the
abnormal parathyroid gland, under protection by bisphosphonate therapy (alendronate, 70 mg/week) and vitamin D supplementation. The patient did not present, however, to the Surgery Department as scheduled.

The patient presented to our Department for another check-up in January 2014, with a somewhat aggravated metabolic profile (tab. II). 25-OH-D level was not re-assessed, but vitamin D supplements were not taken. Despite persistence of primary hPTH, DXA revealed a general increase in BMD following antiresorptive treatment (Lumbar T-score -3.1; Hip T-score -2.7; Forearm T-score -5.1) (fig. 3).

The patient underwent a left inferior parathyroidectomy with the excision of a parathyroid adenoma with a maximum diameter of 1.6 cm (fig. 3). Immediately after excision, PTH dropped to a normal level of 22 pg/ml, confirming an excessive PTH secretion.

The patient had a favorable outcome af-
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ter surgery, with phosphocalcic parameters within normal range after just one day (calcium 9.03 mg/dl, phosphate 3.46 mg/dl, PTH 13.11 pg/ml).

![BMD improvement chart]

**Fig. 3.** BMD improvement after one year of treatment

![Left inferior parathyroid adenoma image]

**Fig. 3.** Left inferior parathyroid adenoma

**DISCUSSION**

Primary hPTH is usually accompanied by hypercalcemia, hypophosphatemia and increased vitamin D level due to excessive 1-alpha hydroxylase activation by PTH. Co-existence of hypovitaminosis D in hPTH may decrease the active intestinal calcium absorption, thereby diminishing serum electrolyte changes (3, 5). Hypovitaminosis D may also contribute to a further tumor growth and increase in PTH secretion due to lower calcium and vitamin D levels and to a consecutive decrease of the negative feedback exerted on the parathyroid adenoma
(3,6-9). This leads to a vicious circle, worsening the renal and bone changes (9, 10, 11).

The higher incidence of hypovitaminosis D in hyperparathyroidism could be explained by several hypotheses. Due to lack of negative feedback, low vitamin D levels may favor the development of an autonomous parathyroid gland, with subsequent occurrence of hyperplasia and adenoma transformation, or accelerated course of a preexisting adenoma (12). PTH-mediated increase of 1,25(OH)₂D may alternately reduce 25(OH)D levels by inhibiting the hepatic synthesis of vitamin D (3).

In our case, hypovitaminosis D partially masked the typical serum metabolic profile of primary hyperparathyroidism, but did not impede the deleterious impact of hPTH on bone loss and kidney stone formation. Delay in diagnosis was also influenced by the additional risk factors for osteoporosis in our patient (age, sex, body mass). PTH tends to be, however, more catabolic at cortical sites, especially at the distal 1/3 of the radius, and this particular modification was also observed in our patient. The association of severe osteoporosis and relapsing renal lithiasis with hypercalciuria increased the suspicion of primary hyperparathyroidism. Despite the persistence of primary hyperparathyroidism, therapy with bisphosphonates had protective effects on bone, but did not diminish PTH levels or improve the metabolic profile of our patient.

CONCLUSIONS

Our case report highlights that when hypovitaminosis D is associated with hyperparathyroidism it masks hypercalcemia, but may aggravate the deleterious effects of the disease on bone loss and on kidney stone formation, so any patient with relapsing lithiasis and/or disproportionately severe osteoporosis should be suspected of primary hyperparathyroidism; if the metabolic parameters are only slightly modified, vitamin D deficiency should be suspected. Vitamin D supplementation in these patients remains a question of debate.

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**TOPICAL METHOTREXATE FORMULATION FOR PSORIASIS TREATMENT**

Psoriasis, a chronic inflammatory skin disease, affects 1 to 3% of the world population. The therapeutic agents used in the treatment of this disease are corticosteroids, dithranol, salicylic acid and vitamin D analogues. The nanostructured lipid carriers (NLCs) play an important role in targeting the drug to the skin. In order to obtain new topical formulations for the treatment of psoriasis, NLCs were used for incorporation of methotrexate. The formulations contained methotrexate, Witepsol S51, oleic acid, Polysorbate 60 (MTX_NLC-P60) or Polysorbate 80 (MTX_NLC-P80). The formulations were tested for their stability by measuring the particle size, the surface charge and the amount of MTX after storage at 25°C for 28 days. Scanning electron microscopy was used to study surface morphology. All formulations showed a high physical stability. *In vitro* skin permeation was evaluated using a Franz cell. The results revealed an increased penetration of MTX_NLC-P60 (5.8 ± 0.2%) and MTX_NLC-P80 (4.2 ± 0.1%) as compared to free MTX (3.6 ± 0.2%). *In vitro* evaluation of drug release from both formulations in a simulated physiological environment showed a quick initial phase of drug release (64%) in the first 2 h, followed by a sustained release until 8 h. The study revealed the potential use of NLCs in the development of topical formulations for psoriasis treatment (Pinto MF, Moura CC, Nunes C, Segundo M et al. A new topical formulation for psoriasis: development of methotrexate-loaded nanostructured lipid carriers. *Int J Pharm* 2014; 477 (1-2): 519-526).

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