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Increased bone modelling as a presentation of Graves' disease

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Summary

The adverse effects of hyperthyroidism on bone have been described for years. Thyroid hormones are necessary for growth, maturation, metabolism and bone remodelling. However, untreated thyrotoxicosis causes increased remodelling, osteopenia or osteoporosis and increased fracture risk. Since the introduction of antithyroid drugs and radioiodine, hyperthyroid bone disease is less common. Here we present a rare case of an asymptomatic patient with thyrotoxicosis making its debut as increased bone remodelling.

Key words: *Graves' disease, bone remodelling, alkaline phosphatase, intact parathyroid hormone.*

Introduction

The biomechanical characteristics of bone depend on the bone mass density (BMD), the microarchitecture and the remodelled bone. An excess of thyroid hormones stimulates remodelling causing a loss of bone due to negative bone balance, with the expansion of resorption cavities and an increase in trabecular perforations. Therefore, untreated thyrotoxicosis can result in osteopenia, osteoporosis and high risk of fractures¹. However, these may also be the consequence of a high risk of falls due to muscular weakness (myopathy) and of an agitated state in some patients. A significant increase in BMD after one year of anti-thyroid treatment has been reported²; however, years of euthyroidism are necessary in order to normalise levels of bone mass^{3,4}.

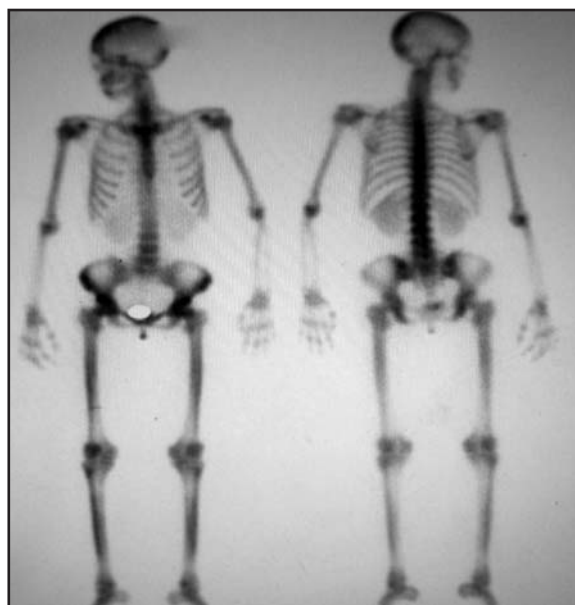
Clinical case

A woman of 33 years of age, native of China, without any medical history of interest, who was referred to the Bone Mineral Disease clinic due to her having been found in a routine analysis to have high levels of alkaline phosphatase. She reported pains in both legs of a month's duration, irregular menstruation and moderate bone loss in recent months. She reported not having had any changes in bowel habits. The physical examination showed no noteworthy abnormalities. Weight, 54 kg; height 1.56 m; body mass index (BMI), 21.39 kg/m². Neck without goitre or palpable adenopathies. In the analysis were observed: haemoglobin, 13.6 g/dl; alkaline phosphatase, 177 UI/l (normal values <120); calcium, 10.2 mg/dl (normal values between 8.2 and 10.6); phosphorus, 3.2 mg/dl (normal values between 2.5 and 5); hydroxycholecalciferol, 12.9 ng/ml (normal values between 20 and 50); intact parathormone (PTH), 36 pg/ml (normal values between 10 and 65), calciuria, 72 mg/24h; tubular reabsorption of phosphates, 89.41%; hydroxyproline/creatinine quotient, 0.278; carboxy-terminal telopeptide of collagen, 1.6 ng/ml (normal values between 0.064 and 0.548); amino-terminal propeptide of procollagen, 388.500 µg/l (normal values between 10.4 and 62); FSH, 9.90 mUI/ml; 17-Beta-estradiol, 25.90 pg/ml; thyroid stimulant hormone (TSH), <0.04 µUI/ml; free T₄, 5.40 ng/dl; and free T₃, >20 pg/ml. Antimicrosomal and anti-thyrotropin receptor (TSHR) positive antibodies.

The thyroid gammagraphy was compatible with diffuse goitre, and the bone gammagraphy showed an increase in diffuse remodelled bone in the cranial shell and at the polyarticular level, without pathological elevations in metabolic activity which would suggest Paget-type disease (Figure 1). A study was completed with a gynaecological review, without evidence of alterations, and a Doppler sonography of the lower limbs, which revealed signs of chronic venous insufficiency.

The patient was diagnosed with primary hyperthyroidism due to Graves-Basedow disease. The patient received treatment with synthetic anti-thyroids (metimazol at decreasing doses) over a

Figure 1. Bone gammagraphy of the patient



period of eighteen months, with which the thyroid function and levels of alkaline phosphatase were normalised. After a subsequent recurrence of the disease some months later, it was subject to definitive treatment with radioiodine.

The increase in bone remodelling was related to the thyroid disease. Currently the patient has clinical and analytic euthyroidism, with levels of alkaline phosphatase within normal limits.

Discussion

Thyrotoxicosis is the clinical syndrome resulting from the exposure of the tissues to an increase in thyroid hormones in circulation. The most common cause is Graves-Basedow disease (GBD) which constitutes 45-60% of all cases of thyrotoxicosis in Europe.

This pathology was described for the first time in 1825 by Parry. However, it took the name of the Irish doctor Robert James Graves, due to his descriptions in 1835, and of Karl Adolph von Basedow, because of his reports in 1840. It is an autoimmune disease defined by the production of antibodies to the thyropin receptor (TSH) in the thyroids. It is characterised by diffuse goitre and thyrotoxicosis, and may be associated with ophthalmopathy and, occasionally, infiltrative dermatopathy.

As is the case with other causes of thyrotoxicosis, GBD is generally associated with an increase in the excretion of calcium and phosphorus in urine and faeces, demineralisation of bone, osteopenia or osteoporosis, an increase in bone remodelling and high risk of fractures¹. In serious cases of thyrotoxicosis hypercalcemia maybe observed. On the other hand, blood concentrations of 25-hydroxycholecalciferol are usually diminished, which contributes to the reduction in the intestinal absorption of calcium, and in some cases, to osteomalacia².

The biochemical markers which reflect bone remodelling may be measured in urine or blood. There are markers for bone resorption, such as tartrate-resistant acid phosphatase, hydroxyproline, pyridinoline, and the N-terminal telopeptides of collagen type 1, and markers for bone formation (proteins synthesised by the osteoblasts), such as osteocalcin, alkaline phosphatase and carboxy-terminal propeptide of type 1 procollagen.

The markers for bone resorption may be increased by up to 7 or 8 times their normal value in patients with hyperparathyroidism⁵. Similarly, osteocalcin and bone alkaline phosphatase, may rise, although to a lesser degree, which suggests an imbalance between bone formation and resorption, with the consequent loss of bone in thyrotoxicosis⁶.

In GBD total blood alkaline phosphatase (AP) is found to be raised in 67% of cases⁷, essentially at the expense of its bone isoenzyme. AP is found in almost all tissues of the body, especially in the intestinal epithelium, renal tubules, bone, liver and placenta. In addition to thyrotoxicosis, there are other pathologies which may raise levels of AP: diseases of the kidney, bone (fractures in repair, bone metastases, sarcoma, myeloma, Paget's disease), liver (biliary obstruction, cholangitis, portal cirrhosis), septicaemia, ulcerous colitis, hyperparathyroidism and malabsorption (which causes a vitamin D deficit). Therefore, the clinical applications of this enzyme are, mainly, in obstructive hepatic disease and in bone metabolic disease, associated with an increase in osteoblast activity.

Increased bone resorption associated with GBD is corrected in 4-8 weeks once the thyroid hormones are normalised⁸. Bone formation, as reflected in the increased concentrations of bone isoenzyme of AP, remains elevated, despite the normalisation of the thyroid function, over a more prolonged period of time⁸.

The singularity of this case resides in its atypical form of presentation of GBD, with few

symptoms of thyroid hyperfunction and with biochemical data compatible with an increase in bone remodelling, which led to the initial discounting of bone metabolic pathology, such as Paget's disease or primary hyperparathyroidism. It is important, therefore, to consider the raised levels of AP in patients with GBD, before and after arriving at euthyroidism, to avoid unnecessary tests and misdiagnoses.

The authors declare that they have no conflict of interest.

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