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Are the current surgical criteria for asymptomatic primary hyperparathyroidism valid?

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Summary

HPTP is a very frequent pathology which often develops asymptotically. Surgical intervention being the only curative treatment for this disease there are some criteria for the indication of surgery, but these do not always fit the reality of the patient since they are based on clinical complications (osteoporosis, renal insufficiency, urolithiasis, fragility fractures).

We present the clinical case of a patient who did not meet any of the requirements for having surgical intervention according to the position documents, and who was operated on after the existence was shown of a deterioration of the trabecular bone structure, determined by the TBS (trabecular bone score) technique, and located in the adenoma using gammagraphy. The possible use of these techniques, not seen in the position documents, to complement the decision regarding surgery, is discussed.

Key words: *primary hyperparathyroidism, diagnosis, consensus, surgery, densitometry, TBS.*

Introduction

Primary hyperparathyroidism (PHPT) is one of the most frequent endocrinopathies, which affects, above all, women over 50 years of age¹⁻⁴. Nowadays, in most of these cases the diagnosis occurs casually, incidental to an analytical study, and the patient is often completely asymptomatic.

In the long term, PHPT may produce a series of complications, such as chronic renal insufficiency, urolithiasis, osteoporosis, fragility fractures and fibrocystic osteopathy¹⁻⁶. On over 90% of occasions PHPT is due to an adenoma and surgery is the only curative treatment^{3,4}. It being preferable to avoid these complications before they occur, there is a discussion as to when it is advisable to intervene surgically in a patient who is clinically asymptomatic. To throw light on this matter a number of position documents have been published⁵⁻¹⁰, without there being unanimous agreement^{2-4,10,11}. Techniques such as bone densitometry help to establish the existence of osteoporosis as a complication^{3,6}, and recently a new technique has been introduced, the trabecular bone score (TBS), which is intended to evaluate the integrity and connectivity of the trabeculae of the vertebrae¹²⁻¹⁵, with some studies having been published which show the early effects of PHPT¹⁴⁻¹⁶.

While intervention criteria are a widely used tool when taking a therapeutic decision, on occasion the patient may benefit from surgery in spite of their not strictly meeting these criteria. We present the case of a patient affected by PHPT, in whom surgery was not indicated by any of the position documents, but in whom there was a deterioration in bone evaluated by TBS, and in whom the adenoma was located by gamma-graphy, with a surgical intervention and a notable clinical and densitometric improvement having been confirmed a year later.

Presentation of Case

A female patient, 57 years of age in 2013, who was referred to our unit for an examination for asymptomatic hypercalcaemia.

It is worth noting from her personal history that the patient was diagnosed with diabetes mellitus type 2 (controlled through diet and oral anti-diabetics), hypercholesterolemia, arterial hypertension and morbid obesity (BMI = 50.5 kg/m²). For these conditions she received statins, metformin and an angiotensin converting enzyme inhibitors (ACEi) She was clinically asymptomatic and the hypercalcaemia was detected by her primary care doctor in the context of a metabolic check-up due to her previous pathologies. She had the menopause at 48 years of age but did not receive hormone replacement therapy following this. She had not suffered fractures.

The existence of asymptomatic primary hyperparathyroidism PHPT having been confirmed due to the presence of high calcaemia, corrected with total proteins, high blood PTH, and having excluded other causes of hypercalcaemia, the patient was submitted for surgery, a right triportal video-

thoracoscope being carried out, the existence of an adenoma being confirmed intra-operationally, which was then resected.

Table 1 gives the analytical data for the patient before, and one year after, surgery, along with the reference values for our hospital.

Table 2 shows the densitometric data, including the TBS before, and one year after, the surgical intervention. The densitometry was carried out using a Hologic® Discovery 4500 densitometer, and the estimation of the TBS was made using the program provided by TBS insights of the Medimaps Group with the same densitometer.

In Table 3 are shown the indication criteria for surgery in asymptomatic primary hyperparathyroidism (PHPT) since 1990 until the last update in 2013, along with the clinical data of the patient.

In Figure 1, the MIBI-technetium 99 gamma-graphy of the parathyroids shows the presence of a focus of high activity in the central thoracic area and situated retrosternally, which suggests the existence of a parathyroid adenoma in the mediastinum. Lastly, in Figure 2, the development is shown of both the DXA and the TBS in the lumbar spine one year after surgery.

Discussion

PHPT is a very common pathology, whose incidence has been estimated as 121 cases/100,000 of the population per year¹, and which is increasing. Primary hyperparathyroidism is being diagnosed increasing early due to the testing for calcaemia in routine analyses, such as occurred in the case we present. Often the patient is completely asymptomatic, and for us this raises the question as to the possible benefit the patient might obtain from surgical intervention²⁻⁴.

From 1990 up until 2014 some criteria have been published by the "Workshop on surgical indications in asymptomatic primary hyperparathyroidism"^{7,5-10}. The clinical and analytical data listed in these are very similar, varying only in some details, such as the change in the densitometric evaluation from the Z-score included in the 1990 criteria⁵ to the T-score from 2002^{6,9}, and the inclusion of fragility fractures from 2008^{6,7}. The last consensus in 2014 included the risk of urolithiasis, either analytical or biochemical, as well as the presence of nephrolithiasis or nephrocalcinosis⁶. On the other hand, age, below 50 years, and hypercalcaemia of 1 mg above the upper limit, have remained unchanged in all the documents. However, some authors suggest that other factors such as baseline PTH, could have greater predictive power of the development of PHPT¹¹.

Our patient did not comply with any of the published criteria for surgical intervention. Nevertheless, we offered her the possibility of surgery for four reasons: a) there was a deterioration in bone microarchitecture, estimated by TBS in the lumbar spine, despite the DXA being normal (Figure 2); b) the adenoma was located in the mediastinum as imaging tests carried out of the parathyroids using MIBI-Technetium⁹⁹, SPECT and

Table 1. Biochemical values obtained in the patient before and after surgery, with the reference values in our Hospital

	20/07/2013	08/07/2014	Reference values
Urea, mg/dl	47	34	10-50
Creatinine, mg/dl	0.7	0.7	0.6-1
GFR MDRD4, ml/m/1,73 m ²	>60	>60	>60
Total calcium, mg/dl	10.9	9.7	8.5-10.5
Corrected calcium, mg/dl	10.9	9.6	8.5-10.5
Phosphorus, mg/dl	3.5	3.3	2.5-4.9
Total protein, g/l	7.2	7.4	6.4-8.4
PTH, pg/ml	117	46.9	15-88
P1NP, ng/ml	36.2	42.2	<37.1
Beta-crosslap, ng/ml	0.52	0.35	0-0.57
Osteocalcin, ng/ml	24.5	14.6	11-43
TRAP, UI/l	2.5	3.2	0-3.3
25 (OH) vitamin D, ng/ml	39.9	26.1	30-80
Calciuria, mg/24h	360	NR	<250

GFR MDRD4: glomerular filtration rate by MDRD4; P1NP: amino-terminal propeptide of procollagen type 1; TRAP: Tartrate-resistant acid phosphatase; NR: not done.

Table 2. Densitometric values of patient before and after surgery. T-score and Z-score obtained from normal values in the Spanish population

	24/07/13	28/03/14	% Annual change
L2-L4 (g/cm ²)	1.109	1.162	4.8*
T-score	0.7	1.2	4.8*
Z-score	2.3	2.9	4.8*
TBS L2-L4 (g/cm ²)	1.145	1.272	16.5*
Total hip (g/cm ²)	1.135	1.098	3.5
T-score	1.6	1.3	3.5
Z-score	2.4	2.1	3.5
Femoral neck (g/cm ²)	0.762	0.789	3.5
T-score	-0.7	-0.5	3.5
Z-score	0.5	0.8	3.5

* Statistically significant change (p<0.05).

Tomo-SPECT suggested (Figure 1); c) having no doubts about the clinical diagnosis or its location it seemed to us improper to wait to see if any complications might appear before intervening; and, d) it is the only curative treatment of PHPT.

A year after having had surgery the patient was clinically asymptomatic. The calcaemia had normalised, the bone mineral density (BMD) had increased in the lumbar spine by almost 5% and the TBS had improved by 16.5%. Therefore, we

Table 3. Criteria for surgical indication of PHPT from 1990-2013

Year (quote)	1990 (2)	2002 (5)	2008 (4)	2013 (3)
Age	<50	<50	<50	<50
Calcemia	>1 mg/dl the upper limit	>1 mg/dl the upper limit	>1 mg/dl the upper limit	>1 mg/dl the upper limit
Clearing creatinine/GF	eGFR reduction >30%	eGFR reduction >30%	eGFR <60 ml/min	eGFR <60 ml/min
Osteoporosis densitometric and/or fracture brittle	Z-Score <-2.0 (specific site)	T-Score <-2.5 (anywhere)	T-Score <-2.5 (anywhere), and/or fracture previous fragility	T-Score <-2.5 (lumbar, hip, femoral neck, distal radius 1/3) and/or diagnosed by image vertebral fracture*
Calciuria 24 hours	>400 mg/dl	>400 mg/dl	>400 mg/dl	>400 mg/dl
Others				Risk of stones or biochemical analy- tical or nephroli- thiasis or nephro- calcinosis presence

GF: glomerular filtration; eGFR: estimated glomerular filtration rate.

* Includes lateral radiograph dorso-lumbar spine, magnetic resonance imaging or computed tomography.

consider that in spite of the patient not meeting the surgical intervention criteria the decision was correct. This leads us to suggest the need to include in the indications for surgery for asymptomatic HPT, on the one hand the evaluation of the TBS, and on the other, the carrying out of a gamma-graphy of the parathyroids, at least as an optional test. Although the measurement of the TBS is a relatively recent technique^{12,13} a number of studies have described its alteration in PHPT^{5,14-16}. We should take into account the fact that the values of TBS may have been affected by the morbid obe-

sity from which our patient suffered, as has been mentioned earlier¹³.

In conclusion, and from the results obtained in this patient, we suggest the need to include, whenever possible, both an estimation of the TBS, as well as a MIBI-Technetium⁹⁹ gammagraphy of the parathyroids, since in the case of a deterioration in bone architecture being observed, or of locating, unequivocally, an adenoma, a surgical indication could be advised. This coincides with the recommendations made by the American Association for Clinical Endocrinology and the American Association of Endocrine Surgery, both of which organisations indicate that "it is unacceptable to have to live with a chronic disease, which in the long term may cause health problems, a disease which could be cured by surgery in the majority of cases"¹⁷.

Conflict of interest: The first author, in the name of the other co-authors, declares that there are no conflicts of interest.

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Figure 1. MIBI scintigraphy Tecnetio⁹⁹ parathyroid showing the existence of a mediastinal adenoma location

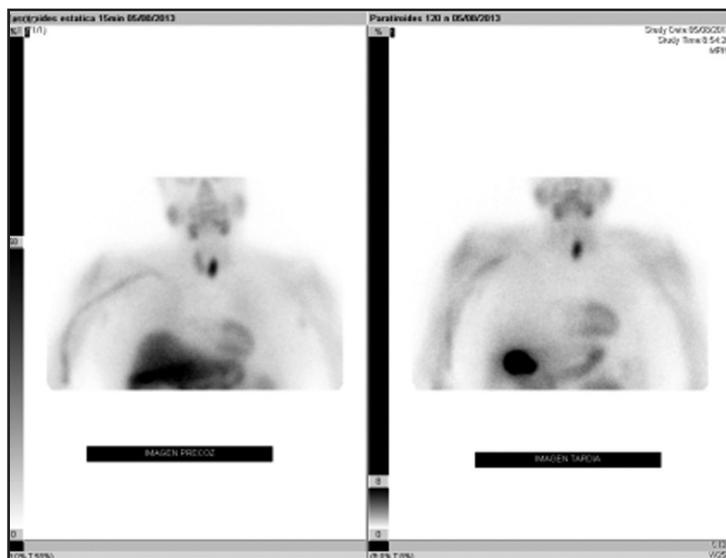
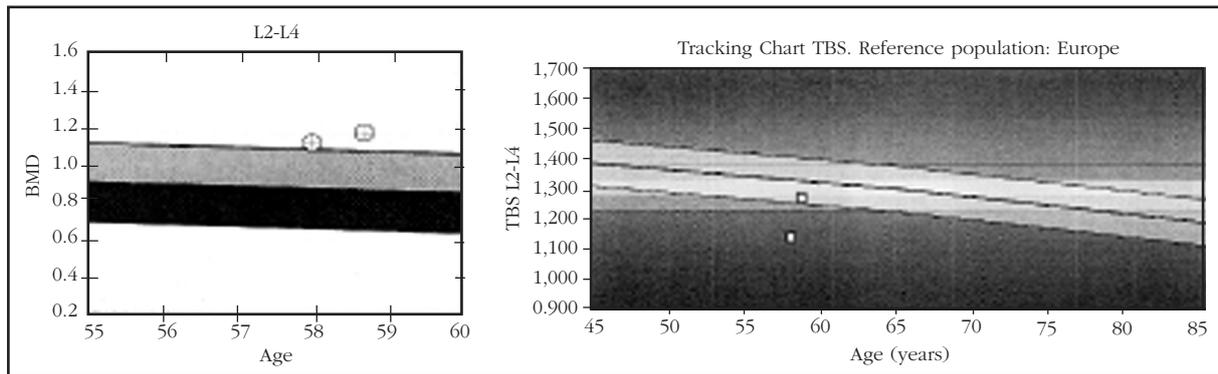


Figure 2. Evolution of the DXA (BMD and TBS) in lumbar spine one year after surgery



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