Parathyroid glands: combination of sestamibi-99mTc scintigraphy and ultrasonography for demonstration of hyperplasic parathyroid glands

E.T.P. Kasa, J.W.E. da Silva, C.A. Mandarim de Lacerda and E. Boasquesivique

Abstract.—Objective. To determine the frequency of the types of parathyroid gland hyperplasia and the sensitivity of sestamibi-99mTc (MIBI) scintigraphy and ultrasonography (US) of patients with secondary hyperparathyroidism (SHPT) due to chronic renal failure.

Material and methods. We studied 43 patients with SHPT (26 females and 17 males with age range of 27-75 years). Blood tests were performed to determine intact parathyroid hormone (PTH), calcium and phosphorus concentration and parathyroid MIBI scintigraphy and US examinations were done, to evaluate each glandular function and structure. Nineteen of the 43 patients underwent total parathyroidectomy and 69 abnormal glands were removed at operation. The 69 abnormal and 4 normal glands from patients that underwent total thyroidecmy were studied by light microscopy. The results were compared and correlation was calculated to: weight, MIBI uptake and US results.

Results. All 43 patients had elevated serum PTH ranged from 400 to 4,075 pg/ml (1,868.0 ± 975.9 and normal range 10-75 pg/ml). Serum calcium and phosphorus concentration were 10.13 ± 2.02 mg/dl and 5.28 ± 2.07 mg/dl respectively. Fifty eight of 69 glands from surgical resection were MIBI positive and 11 were negative, but their cellular composition and presentation were similar. Hyperplasic glands had increased number of all cell types considered (chief, oxyphil and clear) compared to the normal gland. Chief cell hyperplasia was the most frequent type (81%) followed by oxyphil (9%), clear (6%) and adenomatous type (4%). False negative results of 10% to US and 4.6% to scintigraphy were found. The correlation of gland weight and MIBI uptake were not significant (p = 0.09). The sensitivity of MIBI scintigraphy was 84% and US was 72.5%.

Conclusions. The MIBI scintigraphy is a very sensitivity tool for pre-operative localization of hyperplasic parathyroid gland and should be used as the first imaging method. The association of MIBI and US is recommended because increases the sensitivity for preoperative hyperplasic parathyroid glands identification.

KEY WORDS: sestamibi-99mTc, scintigraphy, ultrasonography, parathyrophy, secondary hyperparathyroidism, hyperplasia.

GINDULAS PARATIROIDES: COMBINACIÓN DE LA GAMMA GRÁFICA CON 99mTc-SESTAMIBI Y DE LA ECOGRAFÍA PARA LA DEMOSTRACIÓN DE HIPERPLASIA GLANDULAR

Resumen.—Objetivo. Determinar la frecuencia de los tipos de hiperplasia de glándulas paratiroides y la sensibilidad de la gammagrafía con sestamibi-99mTc (MIBI) y de la ultrasonografía (US) para evaluar pacientes con hiperparatiroidismo secundario (HPTS).

Material y métodos. Fueron estudiados 43 pacientes con HPTS (26 mujeres y 17 hombres con edades entre 27 y 75 años). Fueron determinadas las concentraciones de hormona paratiroides intacta (PTH), calcio y fósforo y evaluada la acumulación total del MIBI en las paratiroides así como la US para evaluación de la estructura y función glandular. En 19 de los 43 pacientes fue realizada resección de 69 glándulas anormales. Las glándulas anormales y 4 normales fueron estudiadas por microscopia óptica. Los resultados fueron comparados y la correlación estimada en relación al peso y a la acumulación de MIBI.

Resultados. El total de los 43 pacientes presentó niveles elevados de PTHi (400-4,075 pg/ml) y los niveles de calcio y fósforo fueron, de media, 10,13 ± 2,02 mg/dl y 5,28 ± 2,07 mg/dl, respectivamente. Cincuenta y ocho de las 69 glándulas resecadas fueron positivas para MIBI y 11 negativas. Sin embargo, la composición celular y su presentación fueron semejantes. Las glándulas con hiperplasia presentaron un número aumentado de todos los tipos celulares. Las células principales fueron el tipo celular que presentó hiperplasia más frecuentemente (81%), seguidas por las células oxifilicas (9%), las claras (6%) y las adenomatosas (4%). Se encontraron resultados falsos negativos en el 10% de las US y en el 4,6% de las gammagrammas. La correlación entre el peso glandular y la acumulación de MIBI no fue significativa (p = 0.09). La sensibilidad de la gammagrafía con MIBI fue del 84% y del 72,5% para la US.

Conclusiones. La gammagrafía con MIBI es una herramienta de alta sensibilidad para la localización de las glándulas con hiperplasia y debería ser utilizada como primera opción de evaluación. Se recomienda la asociación de gammagrafía con MIBI y la US en función del aumento de sensibilidad total con el uso de ambas técnicas.
**INTRODUCTION**

Primary hyperparathyroidism is caused by inappropriate secretion of parathyroid hormone (PTH), which results in hypercalcemia. In 85% or more, the patients present with adenoma in a single parathyroid gland⁴. Hypertrophy of all parathyroid glands and multiple adenomas within the glands account for the remainder of cases.

Secondary hyperparathyroidism (SHPT), on the other hand, is the result of a pathophysiologic response of the parathyroid gland to hypocalcemia in an attempt to maintain calcium homeostasis. The condition can occur because of vitamin D deficiency or low calcium intake. In most instances, however, SHPT is caused by chronic renal failure⁵,⁶. Clinical or surgical treatments to these patients need to be promptly adopted as soon as the disease diagnosis is established in order to avoid many complications. The only effective treatment for SHPT is surgery. The use of imaging techniques in the preoperative localization of the hypofunctioning glands is the subject of controversy⁷-⁹.

The aim of this paper is to assess the sensitivity of sestamibi-⁹⁹mTc (MIBI) scintigraphy and ultrasonography (US) in the localization of lesions causing SHPT and the types of hyperplasia of parathyroid glands and its frequency.

**MATERIAL AND METHODS**

**Patients**

From January 2001 to December 2006, 43 patients (26 women, 17 men; age range 27-75 years) with SHPT due to chronic renal failure, at dialysis program for at least three years, were investigated. All of them had immunoreactive intact PTH, serum calcium and phosphorus measured and parathyroid MIBI scintigraphy. Twenty of the 43 patients underwent US, and 19 had parathyroid gland surgery.

**Imaging studies**

**Scintigraphy imaging**

Planar images of the neck and thorax were performed at 10, 30 and 120 minutes after intravenous administration of 740 MBq (20 mCi) of MIBI, with a gamma camera (E. CAM, Siemens Medical Systems, USA). Images were obtained during 10 minutes counts with a low-energy, parallel hole, high-resolution collimator and a 15% energy window centered on the 140 KeV peak and 256 × 256 matrix. SPECT images were not acquired.

**Ultrasonography**

Twenty patients had high resolution US done by a unique examinator blinded to the MIBI results (10 MHz linear array probe, ATL-3000 Ul, USA). The major three axes of the parathyroid glands were measured and image analysis was performed considering its echo texture, configuration and location in relation to thyroid gland. The volume of the gland was estimated using the ellipsoid formula \((4/3 \times a \times \text{width}^2 \times \text{height})\), where \(a = 3.14159\).

**Histology**

Formalin-fixed parathyroid tissues were sectioned (10 μm thick), stained with hematoxylin and eosin, and examined by the same pathologist. Twelve of the 69 extracted glands had their volume measure by Scherle's method before formalin addition. Clinical, laboratory, and surgical data were taken into account for the final diagnosis of secondary hyperparathyroidism. A qualitative analysis of the glands was performed according to interstitial content and cell types present (chief cells, oxyphil cells, clear cells and fat cells).

All parathyroid glands were classified as hyperplasia according to the criteria suggested by Ghan-dur-Mnayöneh and Kimura, as follows⁴⁰:

1. Chief, oxyphil and clear cell hyperplasia: increased parathyroid mass due to mainly one of these cells proliferation. The foci of nodular proliferation could be surrounded by fibrous tissue as a capsule.
2. Adenomatous hyperplasia: increased gland volume and all cell proliferation, no matter which one was the most frequent. It was considered an advanced stage of secondary hyperplasia characterized by foci of nodular proliferation and sometimes cells arranged in follicular pattern.

**Statistical analysis**

All quantitative data, expressed as mean and standard deviation (SD), were compared using unpaired
Student t-test with \( p = 0.05 \), and linear correlation was evaluated by the Pearson correlation test.

RESULTS

Laboratory data

Patients blood PTH concentration ranged from 400 to 4,075 pg/ml (mean ± SD, 868.0 ± 975.9, normal range 10-75 pg/ml). Serum calcium and phosphorus concentration were 10.1 ± 2.0 mg/dl and 5.3 ± 2.1 mg/dl respectively.

Histology

The frequency of parathyroid gland hyperplasia is presented in the table 1. Considering the 69 studied glands, hemorrhage were found in 11 (16 %), cystic areas in 9 (13 %) and calcification in 1 (1.5 %) of them.

Ultrasonography

All patients that underwent US had parathyroid MIBI scintigraphy too. Fifty parathyroid glands were found (2.8 glands/patient) and two patients had negative results (10 %). Since the glands histology was positive for hyperplasia, they were classified as false negative results (table 2). The US sensitivity was 72.5 % and the positive predictive value (PPV) was 100 %.

Parathyroid scintigraphy

MIBI was positive in 41 patients and 120 glands (2.9 glands/patient). Two patients had negative MIBI (4.6 %), but hyperplasic glands, which made them false negative results. Twenty seven of 43 patients (62.8 %) had three to four positive glands (table 3). Fifty eight glands from 19 patients that underwent parathyroid surgery were positive and 11 were negative (sensitivity of 84 % and a PPV of 100 %). Glan-
dular weight measured by Scherle’s method and MIBI uptake correlation was positive but not signifi-
cant (\( r = 0.52; p = 0.09 \)) (fig. 1).

All type of hyperplasia showed similar uptake of MIBI (fig. 2). Considering all patients, two of them had negative MIBI and US, given a sensitivity of 95 % when considering the combined methods.

Analyzing the 11 glands that presented hemorrhage (11 %), cystic areas (13 %) and calcification (1.5 %), 10 of them did not show MIBI uptake.

Table 1

<table>
<thead>
<tr>
<th>Types of hyperplasia</th>
<th>N (%)</th>
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<tbody>
<tr>
<td>Chief cell</td>
<td>56 (83 %)</td>
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<tr>
<td>Oxyphil</td>
<td>6 (8.7 %)</td>
</tr>
<tr>
<td>Clear</td>
<td>4 (6 %)</td>
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<tr>
<td>Adenomatous</td>
<td>3 (4.3 %)</td>
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Table 2

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of positive glands/patient</th>
<th>Total number of glands</th>
</tr>
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<tbody>
<tr>
<td>5</td>
<td>4</td>
<td>20</td>
</tr>
<tr>
<td>5</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>2</td>
<td>14</td>
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<td>1</td>
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<td>2</td>
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SHPT: secondary hyperparathyroidism.

Table 3

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Number of positive glands/patient</th>
<th>Total number of glands</th>
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</thead>
<tbody>
<tr>
<td>14</td>
<td>4</td>
<td>56</td>
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<tr>
<td>13</td>
<td>3</td>
<td>39</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
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<td>2</td>
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SHPT: secondary hyperparathyroidism.

Fig. 1.—Correlation of the glandular volume and sestamibi-\(^{99m}\)Tc uptake of parathyroid gland (\( r = 0.52 \)).
DISCUSSION

SHPT is a usual complication of chronic renal failure and have been investigated by many groups. Radiological methods (US, parathyroid scintigraphy, computed tomography [CT], magnetic resonance [MR]) were used by many investigators either isolated or in conjunction of two to four of them. Different results of MIBI scintigraphy to evaluate SHPT are found in the literature but studied patient groups are not homogenous when were considered severity of the disease.

Multiple factors have been related to MIBI uptake, including the amount of the chief cells, mitochondria content, glycoprotein P expression and cell cycle phase. However none of these factors alone seems to explain entirely the cell capacity to take up MIBI. The cell types present in hyperfunctioning glands is the most common factor described.

The frequency of chief cell hyperplasia demonstrated in this study is very high and the sensitivity of the MIBI scintigraphy found here is probably dependent of the type of hyperplasia which is in agreement to other investigators’ results. However, positive glands contained other cell types that may have contributed to MIBI uptake too.

Many studies have correlated parathyroid gland volume and MIBI uptake with positive and significant results. In this work, the direct measurement of the glands volume and its MIBI uptake did not have significant correlation; however this may be due to the small number of gland assayed.

Nevertheless, glandular structure must be considered when correlating its volume and function, since the presence of hemorrhage, cystic structures and calcification within the gland can compromise its relative function. Once increase volume due to such structures happens the function may not follow the same way. In the present study, hemorrhage, cystic structures and calcification were found in 16 %, 13 % and 1.5 % of the examined glands, respectively. The positive correlation of gland weight and MIBI uptake found here was not significant and this may have been influenced by the presence of such glandular structures.

Sensitivity, specificity and false positive and negative results of US and scintigraphic examination vary according to retrospective or prospective studies and different works presented in the literature. In this study, sensitivity of MIBI scintigraphy was very similar to that found by other investigator results when it was considered glandular units, however when one consider the patients with positive and negative MIBI sensitivity was significantly higher, but false negative result of US and scintigraphy were lower than those already described.

US is an operator-dependent method. Therefore, this could explain some discrepancies comparing US with scintigraphy in the present study in accordance with literature. The US sensitivity was lower than scintigraphic result and is in agreement with other group results. However, US sensitivity found here was higher than that described in the literature and this may be due to the operator skills.

As demonstrated by US and scintigraphy, the disease progression may produce all glands stimulation with a final result of hyperplasia of many of them. It
was found here 3 to 4 hyperplastic glands in 32.5% of the patients, all of them with very high levels of serum PTH and long time of disease.

The highest sensitivity of parathyroid gland scintigraphy with MIBI compared to US, may be due to the physical principles of each method basis. The scintigraphy mainly evaluates the functional aspect of the gland instead of its anatomical structure. The structure mainly represented by size, echo texture and blood flow is very well done by ultrasound.

The higher sensitivity of the MIBI scintigraphy found here may be related to the advanced state of disease indicated by PTH level and by the high number of chief cell hyperplasia demonstrated in this group of patients.

In conclusion, present results allow us to conclude that the combination of MIBI and US is valuable enhancing the final sensitivity and specificity to the preoperative localization of the hyperfunctioning glands. 11, 12

REFERENCES