THE VOLUME OF SOLITARY PARATHYROID ADENOMA IS RELATED TO PREOPERATIVE PTH AND 25OH-D3, BUT NOT TO CALCIUM LEVELS

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Abstract

Purpose. To correlate the volume of parathyroid adenomas with the hormonal and metabolic profile at patients diagnosed with primary hyperparathyroidism (pHPTH).

Patients and Methods. Cross-sectional multicentric study, enrolling 52 patients with pHPTH from two medical institutions. Serum calcium and PTH were evaluated in all patients before surgery, whereas 25OHD3 was measured only in the 33 patients recruited from one medical unit. The volume of parathyroid adenoma was measured by using the formula of a rotating ellipsoid.

Results. We observed a significant correlation of the volume of parathyroid adenomas with PTH at patients from the two units and in the whole group ($p < 0.0001$), but not with serum calcium ($p = 0.494$). Twenty-five out of the 33 patients at whom 25OHD3 was measured had levels in the range of deficiency. 25OHD3 was not correlated with PTH or calcium levels, but was negatively correlated to the adenoma volume and positively to the PTH/volume ratio ($p = 0.041$ and $p = 0.048$, respectively).

Conclusions. The volume of parathyroid adenoma seems to be related to preoperative PTH and 25OHD3, but not to calcium level. Vitamin D deficiency is frequently found at patients with pHPTH and may contribute to particular disease profiles, including larger parathyroid adenomas.

Key words: parathyroid, volume, correlation, vitamin D, PTH, calcium, hypovitaminosis.

INTRODUCTION

Primary hyperparathyroidism (pHPTH) is caused by the excessive parathyroid hormone (PTH) leading to deleterious impact on calcium and bone metabolism (1, 2). pHPTH has a high incidence in the general population and the main cause is the presence of a solitary parathyroid adenoma (3, 4),

therefore patients can be cured by minimally invasive parathyroidectomy in roughly 90% of cases after previous preoperative localization of the diseased parathyroid gland (5). Once excised, the parathyroid adenoma needs to be histologically confirmed, together with the fast normalization of serum PTH and calcium confirming cure (4, 5). The parathyroid adenoma can be easily weighed (6) and its volume measured (7). There is a wide variation in the dimensions of parathyroid adenomas (8). It is yet not clear whether the dimensions of parathyroid adenomas may influence the sensitivity or specificity of localization techniques (9-12,19), or whether this information may be of value for predicting disease severity (6, 8, 13, 15, 20) or evolution after surgery (6, 8, 13-19, 21-25). The dimensions of parathyroid adenomas were correlated in different studies with various parameters related to calcium and bone metabolism, such as PTH (6,7,14,15, 20, 24-30), calcium (6-8, 13, 15, 17, 24-30), 25OHD3 (14-16,18, 25, 29, 31) or FGF23 (32), but also other biological, histological or genetic findings (33-35), large parathyroid adenomas being described by several authors as having certain particularities (24). Already published data are, however, rather heterogeneous, inconsistent and diverging. The aims of our study were therefore to correlate presurgical metabolic and hormonal parameters with the volumes of excised parathyroid adenomas and thereby to find ways to predict their dimensions.

PATIENTS AND METHODS

We performed a cross-sectional multicentric study involving patients diagnosed with sporadic primary hyperparathyroidism caused by a solitary parathyroid adenoma in two clinical units from Iași and

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Cluj, Romania. The study was approved by the ethical committees of the two hospitals and patients signed an informed consent. A total of 52 patients were recruited from Iași (33 patients between 23 and 77 years of age, mean age of 53.5 ± 12.6 years, 27 women and six men) and Cluj (19 patients between 25 and 78 years of age, mean age of 55.7 ± 12 years, 14 women and five men). Patients with secondary hyperparathyroidism, renal function impairment, parathyroid hyperplasia, double parathyroid adenomas and familial forms of pHPTH were excluded from the study.

A blood sample was obtained from all patients before surgery. Blood was centrifuged and serum was stocked at -30°C for measurement of calcium and PTH (in all patients) and 25OHD3 (only in the patients recruited in Iași). Serum calcium and phosphate were evaluated by spectrophotometry, using Roche commercial kits compatible with the Cobas 6000 automatic analyzer (Roche). PTH was evaluated by chemiluminescence using commercial Siemens kits compatible with the Immulite 2000 automatic analyzer (Siemens). 25OHD3 was measured by ELISA technique, using commercial kits from Immunodiagnostik AG.

All patients were submitted for minimally invasive parathyroidectomy, under general anaesthesia. Three diameters (longitudinal, transversal and sagittal) of the excised parathyroid adenoma were measured with a Hoxel calliper. The volume of the parathyroid adenoma was further calculated by using the formula of a rotating ellipsoid (36). The parathyroid adenomas were further submitted to histological investigation. The cure of the patients was confirmed by intraoperative quick PTH measurement, by using the Miami criteria (4).

We compared the volume of the adenomas with preoperative PTH and calcium in the patients from each surgical unit and in all the patients recruited from both units. We checked the correlations between the adenoma volume of the patients from Iași and 25OHD3

levels. 25OHD3 was also compared to PTH levels as well as with the ratio PTH / adenoma volume.

In order to define high and low PTH and 25OHD3 values in primary hyperparathyroidism, we chose cutoff limits of 250 pg/mL for PTH and of 15 ng/mL for 25OHD3 from the literature (22, 48). We further compared mean volumes of parathyroid adenomas from patients having high or low PTH or 25OHD3, respectively.

Statistical analysis was performed using the SPSS 16.0 software (Chicago, IL, USA). Results were expressed as mean $\pm$ SEM unless otherwise stated. Pearson correlation coefficients were calculated to assess correlations between parathyroid volumes and presurgical PTH, calcium, phosphate and 25OHD3, as well as between 25OHD3 and PTH or PTH / adenoma volume ratios. Student's t test was used to compare mean adenoma volumes from patients with high and low PTH or 25OHD3 levels. Differences were considered significant at p values < 0.05 .

RESULTS

The volumes of parathyroid adenomas were significantly correlated with preoperative PTH, but not with calcium in patients from the two surgical units and in the whole studied group (Fig. 1, Table 1). PTH was not correlated significantly with calcium levels (Table 1).

25OHD3 was evaluated only in the patients from Iași. All but four patients had low or very low levels of 25OHD3 (Fig. 2). While the adenoma volume was positively correlated with PTH in the group of Iași ($p = 0.043$), it was negatively correlated with 25OHD3 ($p = 0.041$) (Fig. 2, Table 2). Serum calcium was not correlated to the adenoma volume, nor to PTH and 25OHD3 (Table 2). Whereas we found no correlation between 25OHD3 and PTH in the group of Iași (Table 2, Fig. 2), 25OHD3 was directly correlated with the ratio PTH / adenoma volume ($p = 0.048$, Fig. 2).

Eighteen patients from Iași had a high PTH ($>$

Table 1. Correlations of various parameters at patients from Iași, Cluj or both clinical units. R - correlation index and p – probability value. Correlation was considered significant at p values < 0.05 (bold, italic)

		Serum PTH	Serum calcium
Adenoma volume	Iași	<i>R = 0.355, p = 0.043</i>	R = 0.012, p = 0.947
	Cluj	<i>R = 0.772, p < 0.0001</i>	R = 0.298, p = 0.215
	Total	<i>R = 0.514, p < 0.0001</i>	R = 0.097, p = 0.494
Serum PTH	Iași	-	R = - 0.082, p = 0.65
	Cluj	-	R = 0.44, p = 0.059
	Total	-	R = 0.284, p = 0.061

Figure 1. Correlations between the volume of parathyroid adenomas and preoperative serum PTH (left) and calcium (right).

Figure 2. Correlations between the volume of parathyroid adenomas and preoperative serum PTH (left) and 25OHD₃ (right) of the 33 patients from Iasi.

Figure 3. Correlations of 25OHD₃ levels with preoperative PTH (left panel) and PTH / adenoma volume ratio (right panel).

250 pg/mL), but the mean volume of their parathyroid adenomas was not significantly higher than the mean volume from the 15 patients having a low PTH (< 250 pg/mL, $p = 0.49$) (Fig. 3). Mean adenoma volume from the 19 patients having low 25OHD3 (< 15 ng/mL) was, however, significantly higher than the mean volume from the other 14 patients with higher 25OHD3 levels (> 15 ng/mL, $p = 0.012$) (Fig. 3). Eleven patients had both high (> 250 pg/mL) PTH and low (< 15 ng/mL) 25OHD3. Mean adenoma volume from these patients was significantly higher than that of the 5 patients having, on the contrary, lower (< 250 pg/mL) PTH and higher (> 15 ng/mL) 25OHD3 ($p = 0.039$) and also higher than mean volume of all 33 patients from Iași, irrespective of their PTH secretory or 25OHD3 repletion status ($p = 0.018$) (Fig. 4).

DISCUSSION

In most of the cases, sporadic pHPH is caused by a solitary parathyroid adenoma and could therefore be cured by minimally invasive parathyroidectomy (4, 5). Predicting the presence of a large parathyroid adenoma and measuring its dimensions after excision may have some clinical importance. Indeed, when the parathyroid adenoma is larger, there is a bigger chance that the

Figure 4. Grey bar - mean adenoma volume of all patients from Iași. Black bars - mean adenoma volume of patients having lower (< 250 pg/mL) PTH and / or higher (> 15 ng/mL) 25OHD3 levels. White bars - mean adenoma volume of patients having higher (> 250 pg/mL) PTH and / or lower (< 15 ng/mL) 25OHD3. $p < 0.05$ compared to opposite group (see text). † $p < 0.05$ compared to the whole group.

lesion is solitary, or at least not hyperplastic (10, 24, 28), although a larger parathyroid adenoma may sometimes mask the presence of a second, smaller adenoma (18). The concordance of an accurate preoperative localization and high preoperative PTH values with the excision of a large adenoma and a rapid decrease of PTH makes the presence of a solitary adenoma very likely (21, 22). Some authors describe the increase of postoperative hypocalcemia risk with larger parathyroid adenomas (6, 24) and lower vitamin D levels (14, 31), whereas others did not observe this relationship (16, 18).

Similarly to most of the authors (6, 8, 14, 17, 20, 24-30), but contrary to a few others (7, 13), we found a positive correlation between presurgical PTH values and the volume of parathyroid adenoma. We did not find, however, any correlation between presurgical calcium levels and the volume of parathyroid adenomas, contrary to data obtained by many authors (6, 8, 13, 17, 24, 26-28, 30) but in accordance with other studies (7, 15, 25). The patients recruited from Iași had very low levels of 25OHD3, many in the range of severe hypovitaminosis. Similar patient features were observed in the studies of Ozbey *et al.* and Al-Hraishawi *et al.* (15, 25). It is possible that vitamin D deficiency buffers the effects of PTH excess on serum calcium levels, by a less efficient vitamin D hydroxylation in the kidney (36), thereby explaining the lack of correlation between presurgical calcium and the volume of parathyroid adenoma. In agreement with this hypothesis and contrary to other authors (8, 24, 25), we did not observe a significant correlation between PTH and serum calcium.

The clinical and pathological spectrum of primary hyperparathyroidism suffered, indeed, a change in time (36), important factors being the precocious diagnosis, an increase in the diagnosis sensitivity (36), but also the increased incidence of D hypovitaminosis (3, 14-16, 37). Romania is a region where D hypovitaminosis seems to be epidemic (38). Although the incidence of vitamin D deficiency increased in younger populations due to modern lifestyle, it is not clear why D hypovitaminosis seems to be even more frequent in hyperparathyroid patients (16, 37).

Table 2. Correlations of various parameters at patients from Iași. R - correlation index and p - probability value. Correlation was considered significant at p values < 0.05 (bold, italic)

	Serum PTH	Serum 25OHD ₃	Serum calcium
Adenoma volume	<i>R = 0.355, p = 0.043</i>	<i>R = - 0.358, p = 0.041</i>	R = 0.012, p = 0.947
Serum PTH	-	R = 0.085, p = 0.638	R = -0.082, p = 0.65
Serum 25OHD ₃	-	-	R = 0.203, p = 0.257

We observed, similar to others (14, 15, 18), a negative correlation between circulating 25OHD3 levels and the volume of parathyroid adenomas. It has been demonstrated that negative feedbacks upon the parathyroid tissue are hampered in the parathyroid adenoma cells (33). However, some negative feedback may be preserved, being dependent on circulating and locally activated 25OHD3 within the parathyroid cells, rather than circulating 1,25(OH)2D3 levels (31). Very low 25OHD3 may therefore lead to the development of larger parathyroid adenomas due to lack of negative feedback on the parathyroid cells from the adenoma.

In line with certain authors (25), but opposite to others (16, 18, 29, 31), we did not find any correlation between 25OHD3 and PTH levels. 25OHD3 was, however, positively correlated with the ratio PTH/ adenoma volume, reflecting PTH secretion per unit of volume. This observation suggests that D hypovitaminosis is accompanied by less PTH secretion per volume unit of adenomas. These data are contradictory to those obtained by Haglund *et al.*, who found that a larger volume is accompanied by a lower PTH mRNA expression per volume unit, but also by high concentrations of 25OHD3 (29). However, in this study there are no data regarding PTH secretion. In another study, contrary to us, Moosgaard *et al.* found that vitamin D status does not influence the volume of parathyroid adenomas, but D hypovitaminosis increases PTH secretion per adenoma weight unit (31). Their study use, however, adenoma weights instead of adenoma volumes. Whereas active vitamin D clearly inhibits PTH gene expression in normal parathyroid cells, VDR expression is profoundly decreased in the cells from parathyroid adenomas (33) and the effects of vitamin D deficiency on autonomous PTH secretion have not been accurately defined. The interplay between vitamin D-mediated effects and the expression or activity of calcium sensing receptor (CaSR) varies in normal or pathological situations (39, 40). In this context, 25OHD3 may further down regulate the expression or sensitivity of calcium sensing receptor (CaSR) in the parathyroid tumor and thereby increase PTH secretion per volume unit.

Our aim was to check whether high PTH and/or low 25OHD3 are good prognostic factors for the presence of a large parathyroid adenoma. There was no significant difference between the adenoma volume from patients with higher (over 250 pg/mL) or lower PTH. Patients with very low 25OHD3 (under 15 pg/mL) had, however, significantly higher parathyroid adenoma tumors. When both conditions were fulfilled,

patients with low 25OHD3 and high PTH had the highest adenoma volumes, significantly higher not only than the adenoma volume of mirror patients, with higher 25OHD3 and lower PTH, but also than the mean adenoma volume of patients from the whole group. This finding suggests that 25OHD3 deficiency has a clear impact on the development of parathyroid adenomas and proposes the simultaneous use of both 25OHD3 and PTH as prognostic factors for the adenoma volume.

We conclude that patients with sporadic pHPTH from a region of vitamin D deficiency have a parathyroid adenoma volume correlated to preoperative PTH, but not calcium levels. 25OHD3 deficiency leads to larger parathyroid adenomas, but PTH secretion per adenoma volume unit may be decreased. The association of high PTH and D hypovitaminosis is prognostic for the existence of larger parathyroid adenomas.

Conflict of interest

The authors declare that they have no conflict of interest.

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