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Significance of Biochemical Parameters in Differentiating Uniglandular from Multiglandular Disease and Limiting Use of Intraoperative Parathormone Assay

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Abstract
Background We studied whether serum calcium and parathormone (PTH) levels are significantly different for uniglandular disease (UGD) and multiglandular disease (MGD) and whether intraoperative rapid intact parathormone (IOPTH) monitoring can be avoided in some cases of minimally invasive parathyroidectomy (MIP) without affecting cure rates, substantiating various previous published studies.
Method This is a single-referral-center retrospective review of prospectively collected data for 281 patients with sporadic primary hyperparathyroidism (sPHPT) from January 1999 to February 2005. The calcium and PTH values were categorized using the following parameters: calcium $\geq$3 mmol/l = 1, <3 mmol/l = 0, PTH $\geq$ 100 pg/ml = 1, PTH < 100 = 1.
Results *P* values for serum calcium and PTH by ANOVA were 0.0547 and 0.3936, respectively, and by the Mann-Whitney test were 0.1606 and 0.6208, respectively. We had 118 patients with concordant technetium 99 m sestamibi scintigraphy (MIBI) and neck ultrasonography (US) and UGD was confirmed in 118 (100%) cases.
Conclusions No significant difference between serum calcium and PTH for UGD and MGD was found. IOPTH monitoring could be avoided when there is concordant positive MIBI and neck US for single, unilateral, hyperfunctioning gland without affecting cure rates.

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Abbreviations

MIP	Minimally invasive parathyroidectomy
BE	Bilateral exploration
sPHPT	Sporadic primary hyperparathyroidism
UGD	Uniglandular disease
MGD	Multiglandular disease
MIBI	Technetium 99 m sestamibi scintigraphy
PTH	Parathormone
US	Ultrasonography
IOPTH	Intraoperative rapid intact parathormone

Introduction

Minimally invasive parathyroidectomy (MIP) by endoscopy or mini-incision is associated with better cosmetic results and reduced morbidity [1–7]. Various studies have established the benefits of MIP. MIP in selected patients has cure rates comparable to bilateral exploration (BE) with the advantages of a smaller incision and reduced pain, operative times, hospital stay, and complications such as injury to the recurrent nerve and permanent hypoparathyroidism [5–7]. MIP has become the treatment of choice for most patients with sporadic primary hyperparathyroidism (sPHPT) who were selected on the basis of preoperative imaging studies [7–9].

To recommend MIP it is necessary to differentiate uniglandular disease (UGD) from multiglandular disease (MGD) preoperatively. Technetium 99 m sestamibi scintigraphy (MIBI) and neck ultrasonography (US) are

localizing studies for the pathologic gland and confirmation by these studies is reliable [10, 11]. The agreement of MIBI and neck US results has very high positive predictive value for UGD [12–17]. We have analyzed whether there is a significant difference between UGD and MGD with respect to serum calcium and parathormone (PTH) levels [18]. At our institute we recommend MIP based on the combined results of MIBI and US with intraoperative rapid intact parathormone (IOPTH) monitoring. IOPTH is a tool that predicts complete resection of all the hyperfunctioning parathyroid tissue during the operation [19–21]. IOPTH is an expensive test [19–21] but selective use of the IOPTH can be substantiated with reduced cost and equivalent cure rates as shown in various studies [13–17].

Methods

This is a single-referral-center retrospective review of prospectively collected data of 281 patients with sporadic primary hyperparathyroidism (sPHPT) from January 1999 to February 2005. Patients with familial hyperparathyroidism, radiation-induced hyperparathyroidism, and parathyroid cancer were excluded from the study. Patients with less than 1-year follow-up were also excluded. Familial hyperparathyroidism was diagnosed by taking a thorough family history and confirmed by genetic testing.

The study consisted of 281 patients. All patients underwent preoperative localizing MIBI and neck US. MIBI was done randomly with single-tracer preferential uptake and retention or dual-tracer subtraction technique but always combined with CT tomography. Neck US was single-operator dependent. Preoperative serum calcium, PTH, and 1,25-dihydroxyvitamin D_3 levels had been recorded for all patients. Biochemical investigations also included serum urea, creatinine, protein, albumin, and alkaline phosphatase. Patients were selected for MIP based on the combined results of MIBI and neck US with IOPTH monitoring. Patients with nonlocalization on MIBI and neck US underwent bilateral exploration (BE). Postoperatively, serum calcium and PTH were recorded on days 1, 2, and 8. The biochemical cure was correlated with the histology report. All patients were followed up with respect to serum calcium, PTH, and vitamin D levels at 1 month, 6 months, and then yearly. The follow-up period was important in providing the cure rates and eliminating persistence and recurrence.

Biochemical parameters for UGD and MGD were compared using the analysis of variance (ANOVA) test for parametric data and the Mann–Whitney test for categorical data. The calcium and PTH values were categorized on the following parameters: calcium $\geq$3 mmol/l = 1, <3 mmol/l = 0, PTH $\geq$ 100 pg/ml = 1, and PTH < 100 = 1 [18].

We used a commercially available IOPTH immunoassay (Nichols Institute Diagnostics, San Juan Capistrano, CA) that uses two polyclonal antibodies directed against the intact PTH peptide. Parathyroid hormone levels were measured at baseline, at skin incision, at gland resection, and at 5 and 15 min following parathyroidectomy. The IOPTH result was considered positive if there was a 50% or greater fall in the PTH level 15 min after ablation of the pathologic gland compared with the highest preablation level [19–21]. We analyzed the need for IOPTH monitoring for positive MIBI, positive US, and concordant positive MIBI and neck US groups.

Results

The study included 281 patients (222 females, 59 males; female:male ratio = 3.8: 1) with a median follow-up of 26 months (range = 12–98 months). The median age for the group was 60.82 years (range = 16.88–89.15 years; mean $\pm$ SD = 60.04 $\pm$ 13.33 years).There were 263 patients (93.6%) with UGD and 18 patients (6.4%) with MGD. The mean preoperative serum calcium for the UGD group was 2.85 $\pm$ 0.23 mmol/l and that for MGD was 2.74 $\pm$ 0.16 mmol/l. The *P* value for parametric data of the calcium level by ANOVA was 0.0547 and that for categorical data of the calcium level by the Mann–Whitney test was 0.1606, suggestive of a nonsignificant difference. The mean preoperative PTH for UGD was 157.33 $\pm$ 145.934 pg/ml and that for MGD was 127.67 $\pm$ 60.79 pg/ml. The *P* value for parametric data by ANOVA was 0.3936 and that for categorical data by the Mann–Whitney test was 0.6208, suggestive of a nonsignificant difference (Table 1).

The sensitivity, specificity, and positive predictive value were calculated using the formulas: TP/(TP + FN), TN/(TN + FP) and TP/(TP + FP), respectively. The MIBI performed at our center had a sensitivity of 84.41% and specificity of 88.89% for UGD. The positive predictive value (PPV) of MIBI was 94.71%. The neck US had a sensitivity of 51.33%, specificity of 66.67%, and PPV of 81.32% for UGD. The concordant positive neck US and MIBI had a sensitivity of 44.87% and PPV of 100% for UGD in our study (Fig. 1).

The group for which preoperative localizing studies were negative consisted of 21 patients, with 9 (42.85%) MGD and 12 (57.15%) UGD.

IOPTH was performed in 241 patients selected for MIP. The result was true positive in 228 and false positive in 1 patient. IOPTH correctly detected eight cases of MGD in the group but also led us to do four unnecessary BE. The sensitivity, specificity, and accuracy were calculated as TP/(TP + FN), TN/(TN + FP), and (TP + TN)/(TP + TN +

Table 1 Important clinical, biochemical, and pathologic parameters of the patients included in the study

Parameters	Values
Total No. of patients (UGD:MGD)	281 (243:18)
Sex (male:female)	59:222
Age (mean ± SD)	60.04 ± 13.33 years
median (range)	60.82 (16.88–89.15) years
Follow-up median (range)	26 months (12–98 months)
UGD, preoperative serum calcium (mean ± SD)	2.85 ± 0.23 mmol/l
median (range)	2.81 (2.44–4.03) mmol/l
UGD, preoperative serum PTH (mean ± SD)	157.33 ± 145.934 pg/ml
median (range)	115 (44–1739) pg/ml
MGD, preoperative serum calcium (mean ± SD)	2.74 ± 0.16 mmol/l
median (range)	2.76 (2.30–2.95) mmol/l
MGD, preoperative serum PTH (Mean ± SD)	127.67 ± 60.79 pg/ml
median (range)	121 (47–300) pg/ml
No. of patients selected for MIP	241 (85.76%)
MIP performed	218 (77.58%)
Pathology: adenoma:double adenoma:asymmetric hyperplasia	243:2:16

UGD uniglandular disease, *MGD* multiglandular disease, *SD* standard deviation

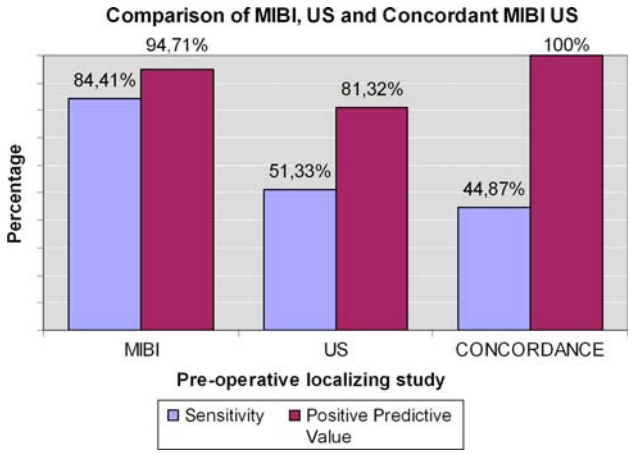

Fig. 1 Comparison of technetium 99 m sestamibi scintigraphy (MIBI), neck ultrasonography (US), and concordant MIBI and US in identifying uniglandular disease (UGD)

Table 2 Statistics for IOPTH results

Parameters	Values
IOPTH performed in patients	241 pts
Result	
True positive[a]	228 pts
False positive	01 pt
True negative	08 pts
False negative	04 pts
Sensitivity: TP/(TP + FN)	98.28%
Specificity: TN/(TN + FP)	88.89%
Accuracy: (TP + TN)/(TP + TN + FP + FN)	97.93%

IOPTH intraoperative rapid intact parathormone, *TP* true positive, *FP* false positive, *TN* true negative, *FN* false negative

[a] IOPTH result was considered positive when there was a 50% or greater fall in the PTH level compared with the highest preablation level at 15 min after resection of enlarged pathologic parathyroid gland

FP + FN), respectively. The results of IOPTH monitoring yielded a sensitivity of 98.28%, specificity of 88.89%, and accuracy 97.93% [19–21] (Table 2).

We had 118 patients with concordant MIBI and neck US and UGD was confirmed in all 118 cases (100%). IOPTH did not serve any function in this group but led us to do one unnecessary BE. There were 147 patients with a score of 3 or greater and in this group 144 patients (98%) had UGD and 3 (2%) had MGD. The patients with a score less than 3 consisted of 134 patients with 119 (89%) UGD and 15 (11%) MGD.

An additional 93 patients with distinct positive MIBI but not picked up by neck US also underwent MIP. Twelve patients who had a very distinct picture on US but whose MIBI was equivocal also underwent MIP. The remaining 20 patients had unilateral topographic nonconcordant localization.

The biochemical cure was achieved in 278 patients (98.93%) after 1 year of follow-up.

Discussion

MIBI and neck US are two mainstay preoperative investigative modalities for localizing parathyroid adenoma and distinguishing UGD from MGD [10–17]. We analyzed the biochemical data for a significant difference between UGD and MGD. The values of serum calcium and PTH were tested for parametric values by ANOVA and were found to

be nonsignificant. The preoperative serum calcium and PTH data were categorized using following criteria: serum calcium $\geq$ 3 mmol/l = 1, <3 mmol/l = 0, serum PTH $\geq$ 100 pg/ml = 1, and PTH < 100 = 1 [18]. The difference was found to be nonsignificant for preoperative calcium and PTH in differentiating UGD from MGD, although mean and median values were higher for UGD compared to MGD. There were 147 patients with a score of 3 or greater and in this group 144 patients (98%) had UGD and 3 (2%) had MGD. Patients with a score of less than 3 consisted of 134 patients with 119 (89%) UGD and 15 (11%) MGD.

Of the 147 patients with a score of 3 or greater, 118 patients had concordant MIBI and neck US; thus, for remaining 29 patients in this group, 2 points were added due to serum calcium $\geq$ 3 mmol/l and serum PTH $\geq$ 100 pg/ml. All patients who had concordant MIBI and neck US were confirmed with UGD, but in 29 patients, who were included due to serum calcium and PTH, there were three cases of MGD, leading to a failure in 10.34% cases. Thus, in our patient group biochemical parameters were not at par with localizing studies for differentiating UGD from MGD.

For the 93 patients with distinct positive MIBI but not picked up by neck US, the scoring system could identify only 26 (30%) UGD, while this group had 87 confirmed cases of UGD. Thus 61/87 (70%) of the remaining confirmed positive UGD patients were not picked up by biochemical parameters. At the same time, 3 (11.34%) cases of MGD were also picked up as false–positive cases. Results indicate more significance for distinct positive MIBI rather than the combined effect of the scoring system point for serum calcium and PTH.

The scoring model proposed by Kebebew et al. [18], which includes serum calcium and PTH for differentiation of UGD and MGD, does not hold well when applied to our patients. Anatomical and functional studies are the main stay in differentiation. These findings at our referral center could be due to early diagnosis of sPHPT, which leads to a reduction in the difference of the biochemical parameters between of UGD and MGD [22, 23]. The MGD group was very small in our study which could affect the statistical significance of the results.

There is trend toward early diagnosis of hyperparathyroidism with the increasing awareness of parathyroid disease and calcium level monitoring in the general population. When diagnosed early in the clinical history of the disease, patients with UGD are managed at a relatively lower level of calcium and PTH than those diagnosed late in the clinical history of the disease with prolonged symptoms or complications [22, 23]. This trend may obviously lower the difference in the biochemical parameters for UGD and MGD.

IOPTH monitoring is expensive. Selective use of IOPTH could be substantiated with equivalent cure rates and reduced cost. We found that almost all cases who had undergone concordant MIBI and neck US had UGD, and IOPTH monitoring in this group could have been avoided without affecting cure rates [13–17].

Patients were selected for MIP based on concordant localization on MIBI and neck US or distinct positive MIBI or distinct positive neck US with equivocal MIBI. CT tomography gives important information about the location of the hyperfunctioning gland, and it can be correlated with embryologic positioning of the gland. Comparison of MIBI tomography with neck US gives clearer picture of the pathologic gland with exclusion of tracer retention by the thyroid nodule. Dedicated single-operator neck US can be a highly reliable anatomical localizing study. With the demonstration of US and color Doppler characteristics of the pathologic gland, neck US films can give the exact location of the adenoma and could suffice for MIP [13–17].

Conclusion

No significant differences between serum calcium and PTH for UGD and MGD were found at our referral center and thus biochemical parameters were not significant in differentiating UGD from MGD. IOPTH monitoring could be avoided in cases of concordant positive MIBI and neck US findings for a single, unilateral, hyperfunctioning gland without affecting cure rates and with the benefits of cost saving and avoidance of unnecessary BE in false–positive IOPTH results.

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