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ORIGINAL ARTICLE

Can we predict expected adenoma weight preoperatively with reference to the correlation of preoperative biochemical tests with parathyroid adenoma weight?

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KEYWORDS
Primary hyperparathyroidism;
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Summary *Background:* Primary hyperparathyroidism is a prevalent disease with proven benefits for appropriately selected patients who undergo parathyroidectomy. The ability to accurately predict expected single adenoma gland weight as the cause based on preoperative biochemical tests could improve cure rates in a minimally invasive approach.
Objective: To assess the correlation between parathyroid weight and preoperative parathyroid hormone and calcium levels in patients with primary hyperparathyroidism with a solitary adenoma and determine if these could be used to predict expected parathyroid weight.
Methods: Patients with primary hyperparathyroidism who underwent curative parathyroidectomy from 2013 to 2018 was retrospectively analysed.
Results: There is a strong positive correlation $r = 0.602$ between preoperative PTH levels with respect to parathyroid weight ($p < 0.001$). There was a moderate correlation $r = 0.474$ between preoperative adjusted Calcium and PTH weight ($p < 0.001$). An algorithm was developed to calculate predicted weight of a single adenoma but when tested against cases with hyperplasia and double adenomas during the period, the variability of predicted weight meant it was impossible to differentiate between the causes. Hyperplasia was excluded and 95% of double adenomas excluded however, when parathyroid weight exceeded 1200 mg
Conclusion: There is a strong correlation between preoperative PTH levels and calcium levels with parathyroid weight. The large variability of predicted parathyroid weight however, precludes the use of biochemical tests alone preoperatively in being able to differentiate between a single adenoma, double adenoma or hyperplasia as the cause in primary

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hyperparathyroidism. At parathyroid predicted weights above 1200 mg however, all cases of hyperplasia, and 95% of double adenomas excluded.

1. Introduction

Primary Hyperparathyroidism (PHPT) is a prevalent disease in the population at 7 cases per 1000 adults.[1] A solitary parathyroid adenoma is the cause in most cases (85–90%) with the remaining being multiple adenomas, hyperplasia and rarely carcinoma. Most people (85–90%) have four parathyroid glands each of mean total weight 29.5–62.4 mg.[2,3] Normal gland dimensions are 3–6 mm (length) by 2–4 mm (width) and 0.5–2 mm (thickness).[4] Primary Hyperparathyroidism (PHPT) is commonly associated with renal calculi, osteopenia, osteoporosis, constipation and other mental side effects.

The benefits of curative parathyroidectomy are well documented with the highest chance of cure at the index operation.[5] In re-explorations, there is considerable increase in morbidity with a decreased chance of cure.[6] Thus, the ability to predict the minimum expected weight of the gland accurately could be valuable to the operating surgeon in a minimally invasive approach. The correlation between preoperative calcium, PTH levels and parathyroid adenoma weight remains indeterminate. Some studies report a statistically significant correlation between preoperative calcium, PTH and parathyroid weight[7–10] whereas others dispute the finding.[11,12] Many of these papers published consist of small numbers which may account for the variable findings. This study aimed to investigate the correlation between preoperative calcium and PTH levels with respect to parathyroid histological weight and volume and analyse its ability to predict single adenoma weight as the cause in primary HPT with a large database.

1.1. Ethical considerations

Ethical approval was obtained through the Ethics Committee via St John of God Hospital.

2. Methods

Data entered prospectively was analysed retrospectively from the Western Australian Endocrine Database from January 2013 to December 2018 from three surgeons. All patients underwent a parathyroidectomy with either a bilateral cervical exploration or minimally invasive approach. All patients had histological confirmation of a single adenoma with parathyroid weight obtained from histological records. Preoperative peak PTH and Calcium levels were used in the analysis. Initially 621 patients were identified. Patients who had double adenomas, gland hyperplasia, parathyroid carcinoma, recurrent or persistent hyperparathyroidism were then excluded from the initial analysis. After applying exclusion criteria and patients with incomplete blood tests, a total of 555 patients were included for analysis.

2.1. Statistical analysis

Exploratory data analysis was initially conducted. Descriptive statistics for each of the variables of interests were given by mean and standard deviation (SD), along with the minimum and maximum values. Correlation and linear regression analyses were conducted to ascertain the relationship between parathyroid (PT) weight (mg) as a dependent variable with calcium (mmol/L) and parathyroid hormone (PTH) levels (pmol/L) as instrumental variables including age as a confounding variable. Scatter plots were used to examine the nature of the relationship between the instrumental variables with PT weight visually. Log-transformed PT weight and PTH level were used in the models. There was a log–linear relationship between the variables.

The association between each of the instrumental variables (IVs) with PT weight was initially investigated with simple linear regression modelling. The significance of the IVs was then examined simultaneously using a multivariable linear regression model. All analyses were conducted using IBM SPSS. Statistical significance was defined as $p \leq 0.05$.

3. Results

A total of 555 patients were included for statistical analysis. The summary statistics for PT weight and the relevant predictors are given in Table 1. Fig. 1 and Fig. 2 illustrate the bivariate relationship between PTH level with PT weight and calcium. The variability in PT weight increased with PTH level, especially when PTH exceeded 50 (Fig. 1). This behaviour for PT weight was also evident when calcium level exceeded 3 mg/dL. Nevertheless, PT weight had a linear relationship to PTH levels and calcium.

The results for the correlation and regression analyses are presented in Table 2. Both univariable and multivariable analyses show that PTH level and calcium are significantly and linearly associated with PT weight ($p < 0.01$), where PTH and calcium levels increased with increasing PT

Table 1 Summary statistics of the relevant DV and IVs.

Variable	Mean (SD)	Range (min, max)
PT Weight	1022 (2310)	(38, 31700)
PTH Level	17.9 (23.3)	(4.5, 369.2)
Calcium	2.71 (0.21)	(2.26, 3.91)
Age in years	63.3 (13.6)	(17, 93)

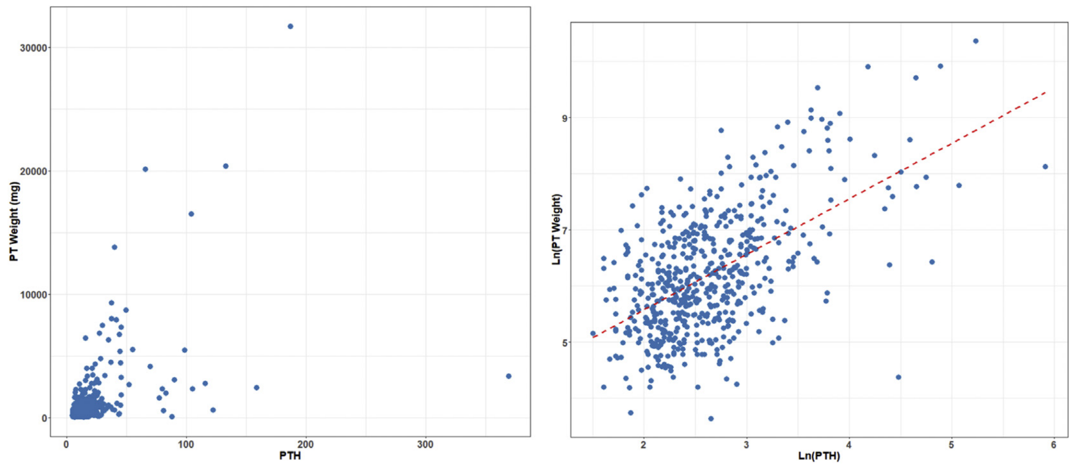

Figure 1 Scatter plot of PT weight vs PTH, untransformed (left) and log-transformed (right). The broken red line represents the regression line.

weights. Of the two predictors, PTH level has a stronger correlation with PT weight than calcium. Age was found to be negatively associated with PT weight.

Fig. 3 provides a visual diagnostic of the multivariable model. The scatterplot demonstrates strong significant correlation (Pearson $r = 0.602$, $p < 0.001$) between observed PT weights and the PT weight estimates from the multivariable model. The residual plot (right) illustrates normal behaviour from the residuals.

Based on the data and analysis, we developed an algorithm (PT Weight = Exp (1.8581 + 0.86213*Ln (PTH level) + 1.0159*Calcium − 0.01096*Age) that would calculate the expected weight as well as minimum weight for a solitary adenoma based on preoperative calcium and PTH levels (CI 95% $p < 0.001$) (Fig. 3). The formula was then tested against all cases of hyperplasia and double adenomas during the same time period. A total of 71 (10.3%) double adenoma and 63 (9.2%) hyperplasia cases were identified. These were plotted in the multivariate regression model and ROC analysis conducted (Fig. 4). With an AUC = 0.506, the predicted PT weights had no capacity to distinguish between single adenoma and double adenoma (Fig. 5). However, there was moderate ability to distinguish single adenoma from hyperplasia (AUC = 0.691). A specificity of 95% was achieved at the cut-off of PT weight at 759 mg with a predictive positive value (PPV) of 97%. Furthermore, if PT gland weight was greater than 1200 mg, 95% of double adenomas and 100% of hyperplasia cases were excluded.

4. Discussion

Previous research exploring the relationship between preoperative biochemical results and parathyroid weight have concluded with discrepant findings. We analysed 555 patients and demonstrate a strong positive correlation 0.557 between preoperative PTH levels with respect to parathyroid weight ($p < 0.001$). There was a moderately significant correlation 0.466 between preoperative adjusted Calcium and PTH weight ($p < 0.001$). The correlation of parathyroid weight with PTH levels was stronger than adjusted calcium with an overall strong Pearson correlation at 0.602 ($p < 0.001$). Bindish et al described a positive correlation between single adenoma weight and volume.[8]

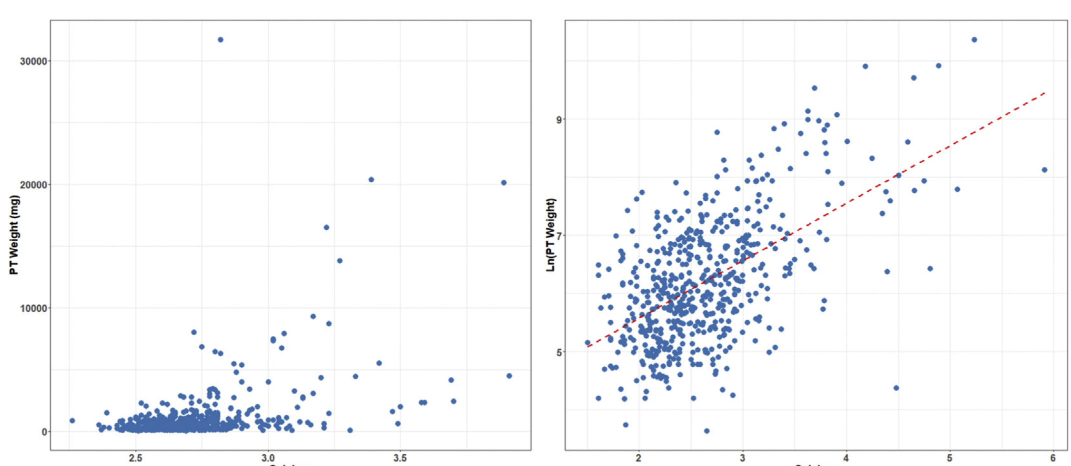

Figure 2 Scatter plot of the untransformed (left) and log-transformed (right) PT weight vs Calcium. The broken red line represents the regression line.

Table 2 Univariable and multivariable linear regression modelling of log-transformed PT weight with PTH level, calcium and age.

	Univariable[a]			Multivariable[b]		
Predictor	Correlation	Estimate (95% CI[c])	*p*-value	Partial Correlation	Estimate (95% CI[c])	*p*-value
Ln (PTH Level)	0.557	0.99 (0.87, 1.11)	<0.001	0.402	0.75 (0.61, 0.89)	<0.001
Calcium	0.466	2.37 (1.99, 2.75)	<0.001	0.238	1.20 (0.79, 1.61)	<0.001
Age[d]	0.138	−0.05 (−0.09, −0.02)	0.001	−0.160	−0.05 (−0.08, −0.02)	<0.001

[a] Ln (PT weight) was modelled against each predictor independently of the others.
[b] Ln (PT weight) was modelled against all the predictors simultaneously. Adjusted R^b = 0.359.
[c] CI = Confidence interval.
[d] Estimate and 95% CI for Age are given for every 5-year increment.

Moretz et al found a positive correlation between intraoperative PTH and parathyroid weight only when the PTH levels were high or low.[9] Kamani et al looking at 69 patients demonstrated a positive correlation between PTH weight and preoperative PTH levels and calcium but not phosphate.[10] Other studies which looked at 40–77 patients showed no correlation between preoperative biochemical results and parathyroid weight or volume.[11,12] The largest study by Stern et al looking at 371 patients found a significant correlation between preoperative PTH level, preoperative calcium with parathyroid weight and volume.[7] This article was also unique as they examined the possible correlation between chief cell proportion histologically and PTH level but found no statistically significant correlation.[7]

Parathyroid weight and percentage of functional cells.[13] The variability of a parathyroid adenoma weight for a given PTH level can be affected by fibrosis, calcification, haemorrhage and cystic degeneration.[14] The proportion of functional cells is also a potential reason for the large variability in weight for a given PTH level.[7] Apart from percentage of functional cells, another theory for variability in PTH weight is vitamin D deficiency. Vitamin D deficiency has been described to result in heavier adenomasBased on these findings, we initially developed an algorithm to calculate expected parathyroid weight of a single adenoma as a cause based on preoperative biochemical calcium and PTH levels. Being able to predict expected weights could be useful particularly where intraoperative parathyroid hormone measurement (ioPTH) is not utilised routinely. It has been well documented that an appropriate ioPTH fall increases surgical curative rates particularly in a minimally invasive approach.[15] Intraoperative PTH is not routinely performed in our surgical centres and most of Australia and New Zealand due to a slow turnover time. Unfortunately, when we simultaneously analysed patients with hyperplasia and double adenomas within the same time period with the algorithm, it was impossible to differentiate between the three based on predicted weight (Fig. 4). The significant finding however, was that at parathyroid predicted weights above 1200 mg, all cases of hyperplasia were excluded and 95% of double adenomas excluded.

In this study, we found that variability of predicted PT weight increased with higher preoperative PTH and calcium levels. This variability in predicted PT weights accounts for the difficulty in accurately predicting intraoperative weight despite strong linear correlation on a regression model. One of the causes of variability is.[16]

This study is limited by its retrospective design, relatively small sample size and that we defined cure as a significant drop postoperatively to a low normal PTH level as well as normal calcium and parathyroid hormone level at two weeks postoperatively. We were unable to account for repeated tests for the majority of these patients at 6

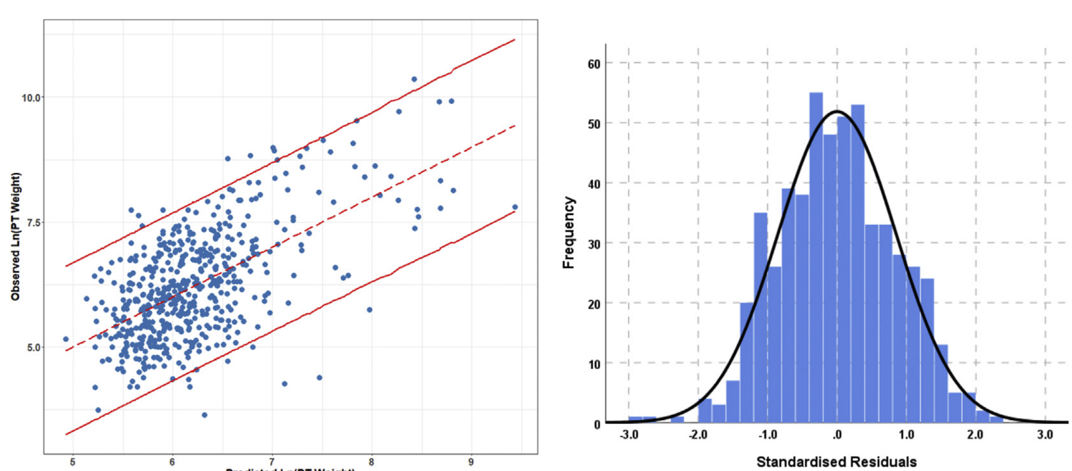

Figure 3 Scatterplot (left) of the observed PT weights and the multivariable model estimates and the residual plot (right). The broken red line on the scatterplot represents the model estimates with the solid lines representing the 95% prediction interval.

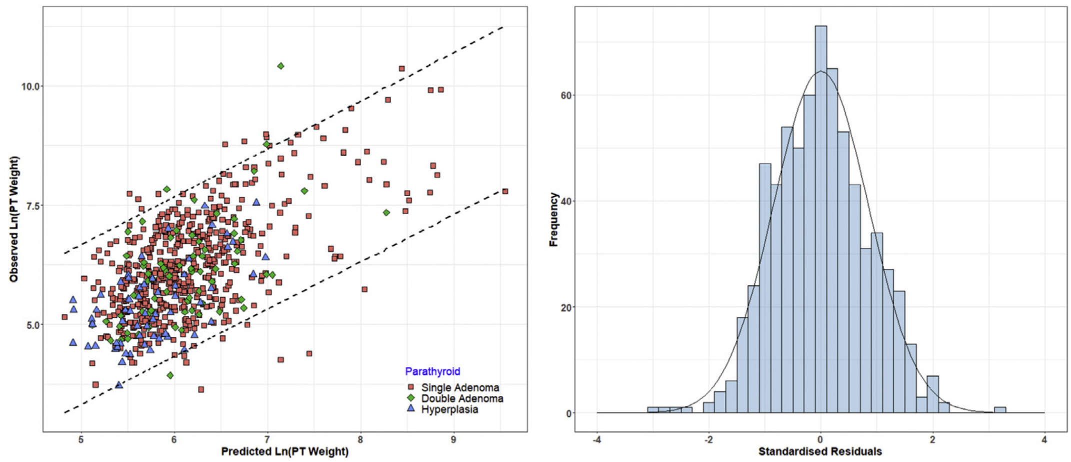

Figure 4 Scatterplot (left) of the observed PT weights and the multivariable model estimates and the residual plot (right) including hyperplasia and double adenoma. The black broken line on the scatterplot represents the 95% prediction interval.

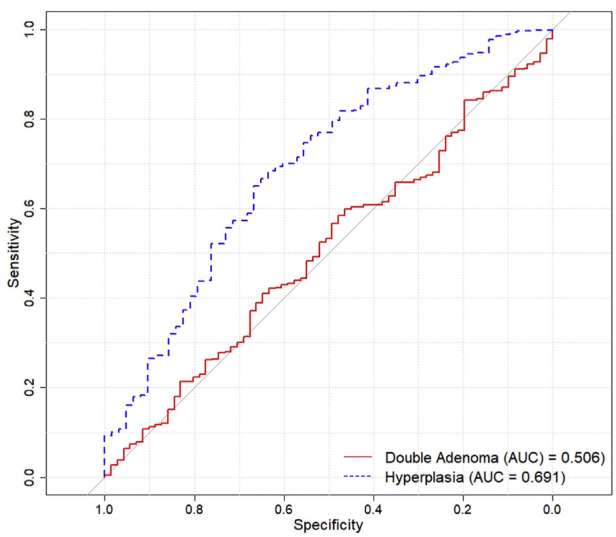

Figure 5 ROC curves showing the predicted PT weights had no separation capacity in relation to double adenoma, however, had moderate ability to differentiate single adenoma from hyperplasia.

months. We acknowledge that up to 3–5% of persistent hyperparathyroidism could potentially be missed in this scenario.[17] All of these patients however have not had re-operations registered in the database, which encompasses the majority of parathyroid surgery done in Western Australia. Another limitation is that the labs that test for PTH vary in using either Centaur or Roche for analysis. The intervals for PTH used by Centaur is 1.9–8.5 pmol/L and Roche 1.6–6.9 pmol/L.

5. Conclusions

This study shows that there is a strong positive correlation between PTH weight and preoperative PTH Levels and a moderate positive correlation to preoperative calcium levels. The variability of parathyroid weight however, precludes the use of biochemical tests alone preoperatively in being able to differentiate between a single adenoma, double adenoma or hyperplasia as the cause in primary hyperparathyroidism. At parathyroid predicted weights above 1200 mg, all cases of hyperplasia, and 95% of double adenomas excluded.

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Declaration of Competing Interest

None.

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