Original Research
Medical Journal of Islamic Republic of Iran, Vol. 25, No. 3, Nov. 2011, pp. 136- 141

Adenoma weight and biochemical parameters in primary hyperparathyroidism

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Received: 6 Jan 2011 Revised: 26 Feb 2011 Accepted: 29 May 2011

Abstract

Background: Primary hyperparathyroidism is autonomous production of parathyroid hormone. After removal of adenoma, one of the surgeons concern is postoperative hypocalcaemia. There is no precise method to determine if patients have hypocalcaemia postoperatively. The purpose of this study was to determine the relation between parathyroid adenoma weights, postoperative serum calcium and serum biochemical parameters in patients with primary hyperparathyroidism.

Methods: In a prospective study, eighty patients with single parathyroid adenoma were enrolled. Preoperative serum levels of calcium, phosphate, PTH, as well as Postoperative serum calcium and weight of adenomas were recorded. The level of significance was set to be $p < 0.05$.

Results: There was no significant correlation between postoperative serum calcium, parathyroid adenoma weight ($r= -0.17$, $p= 0.1$), and parathyroid hormone level ($r = -0.11$, $p = 0.3$). However, a weak correlation between postoperative and preoperative serum calcium levels ($r = 0.23$, $p = 0.03$) was observed. Moreover, Serum calcium decline after adenoma resection was statistically correlated with adenoma weight ($r = 0.36$, $p= 0.001$), preoperative serum calcium ($r = 0.92$, $p= 0.0007$), PTH ($r= 0.54$, $p= 0.0005$) and ALP levels ($r = 0.3$, $p= 0.006$).

Conclusion: Although preoperative serum markers and adenoma weight are unreliable in predicting postoperative serum calcium level, it is possible to estimate postoperative calcium decline by considering adenoma weight and preoperative serum biochemical parameters.

Keywords: primary hyperparathyroidism, adenoma weight, biochemical markers.

Introduction

Primary hyperparathyroidism is a condition characterized by inappropriate excess secretion of parathyroid hormone (PTH), leading to hypercalcemia, hypophosphatemia and mild hyperchloremic acidosis [1]. It occurs in one of every 500 women and one of every 2000 men over 40 years in USA [1]. Single parathyroid adenoma is the etiology of primary hyperparathyroidism in approximately 85-90% of patients [2]. The normal parathyroid gland is an oval shape, approximately 6 mm in size and weighs up

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to 60 mg. There are usually four glands, but the number of glands in any patient can vary between two to six [3].

The variability in the number and position of the parathyroid glands, their small size, and the morphological similarity between normal and pathological tissues makes parathyroid surgery a challenging operation [4]. The ability to predict the size and identify the approximate location of a parathyroid adenoma can therefore greatly assist the operating surgeon. However, despite the availability of a wide array of imaging and endocrinological investigations, which include scintigraphy, ultrasonography, computed tomography, magnetic resonance imaging, parathyroid selective venous sampling and intra-operative PTH assays, no single investigation has been shown to reliably identify parathyroid adenomas in all cases [3,5].

It has been hypothesized that the size of a solitary parathyroid adenoma may be predictable from the preoperative serum levels of PTH, calcium or phosphate [6]. So far, there has been controversy on relationship between preoperative biochemical parameters (including serum calcium, phosphate, alkaline phosphatase, and PTH) and parathyroid adenoma weight and/or postoperative serum calcium. To date, different retrospective studies have reported various results. We designed this prospective study to evaluate several markers in search for potential prediction of parathyroid adenoma weight. If such a correlation exists, it helps the surgeon to formulate a sense of size of the adenoma during operation. Since, exploration is the gold standard for localizing parathyroid adenoma during the first surgical operation, ability to predict adenoma weight should be helpful concerning what to expect during the surgery. The second aim of the study was to evaluate factors that can potentially alter postoperative serum calcium level. This correlation helps surgeons to predict which patients will most probably become hypocalcemic postoperatively and so to manage them accordingly.

Methods

In a prospective study from 2005 to 2007, we enrolled patients with primary hyperparathyroidism who underwent parathyroidectomy based on NIH criteria in Shariati Hospital (Tehran University of Medical Sciences). Exclusion criteria were secondary operations, parathyroid hyperplasia, multiple adenomas, and parathyroid carcinoma. Factors affecting postoperative serum calcium level such as preoperative serum alkaline phosphatase, serum calcium level, PTH level and adenoma weight were evaluated for their effect on postoperative serum calcium level. Eighty patients with single parathyroid adenoma were opted for the study. Demographic data as well as preoperative serum calcium, phosphate, PTH and ALP were recorded. Blood parameters were measured within 2 weeks of surgery. Localization of parathyroid adenoma was done by sestamibi scan and ultrasonography in all patients. All scintographies were done in one center and all sonographies were done by one experienced faculty radiologist before operation. All patients underwent resection of parathyroid adenoma by a single surgeon. During the operation, all the parathyroid glands

Table 1. Patients' characteristics and preoperative markers.

Number of patients	*80*
Age (yr) (mean ± SD)	48 ± 14
Female or male ratio	4
Preoperative markers (mean ± SD)	
Preoperative Calcium (mg/dl)	11.3 ± 1.4
Phosphate (mg/dl)	2.47 ± 0.52
Parathyroid hormone (ng/L)	451.6 ± 137.8
Alkaline phosphatase (IU/l)	571.75 ± 163
Adenoma weight (gr)	2.6 ± 2.2
Postoperative calcium (mg/dl) (mean ± SD)	8.5 ± 0.6

were explored and adenomas resected completely. Adenoma weight was measured in milligrams in the operating room. Parathyroid adenoma was confirmed by frozen section. Postoperative serum calcium was measured 24 hours after surgery. Calcium supplement was given for patients with hypocalcemic symptoms or if serum calcium level was below 8 mg/dl. The ratio of PTH release to weight of adenoma has been considered as an estimate of adenoma's function by Williams et al [17] and Hamidi et al [6]. We also calculated this parameter by dividing serum PTH level by adenoma weight and named it PTH density.

Statistical Analysis

The results are presented here as statistical means with standard deviation or binomial percentages where appropriate. Bivariate Pearson correlation and Independent sample T-test were performed in univariate analysis of baseline characteristics. Moreover, linear regression was used to test relationship between biochemical markers, adenoma weight and postoperative serum calcium. Statistical analysis was carried out using SPSS version 17 (SPSS Inc. Chicago, IL, USA) and $p<0.05$ was considered statistically significant.

Results

Of 80 enrolled patients, sixty four (80%) were women (the male to female gender distribution was 1: 4). The mean age was 48±14 years. Adenoma weight ranged from 0.4 to 10 grams (mean 2.6±2.2). Table 1 provides more information on patients' demographic, preoperative, postoperative biochemical data, and adenoma weight.

Correlation between adenoma weight and other parameters

We found no association between adenoma weight and patient's age (bivariate correlation) and sex (t-test). However, adenoma weight had a positive correlation with preoperative serum calcium ($r= 0.3$, $p= 0.003$), PTH ($r= 0.61$, $p= 0.0001$) and ALP ($r = 0.43$, $p= 0.0005$). No association between preoperative serum phosphate and adenoma weight was detected ($r= -0.14$, $p = 0.2$) (Fig. 1). It should be emphasized that although correlation between adenoma weight and preoperative serum calcium was significant, but overally it was weak. The correlation coefficient was only significant for PTH. In multiple regression, we evaluated the effect of preoperative serum calcium, ALP and PTH level on adenoma weight. Only the effect of PTH and ALP was statistically significant with $p<0.001$.

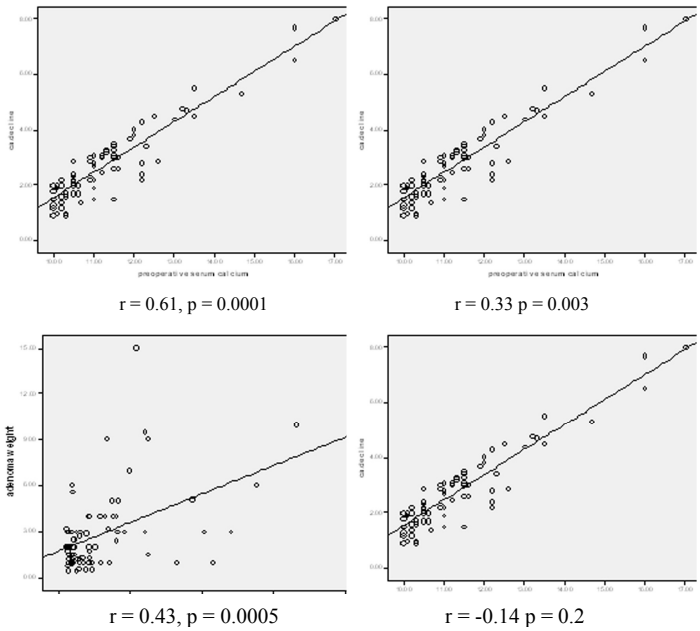
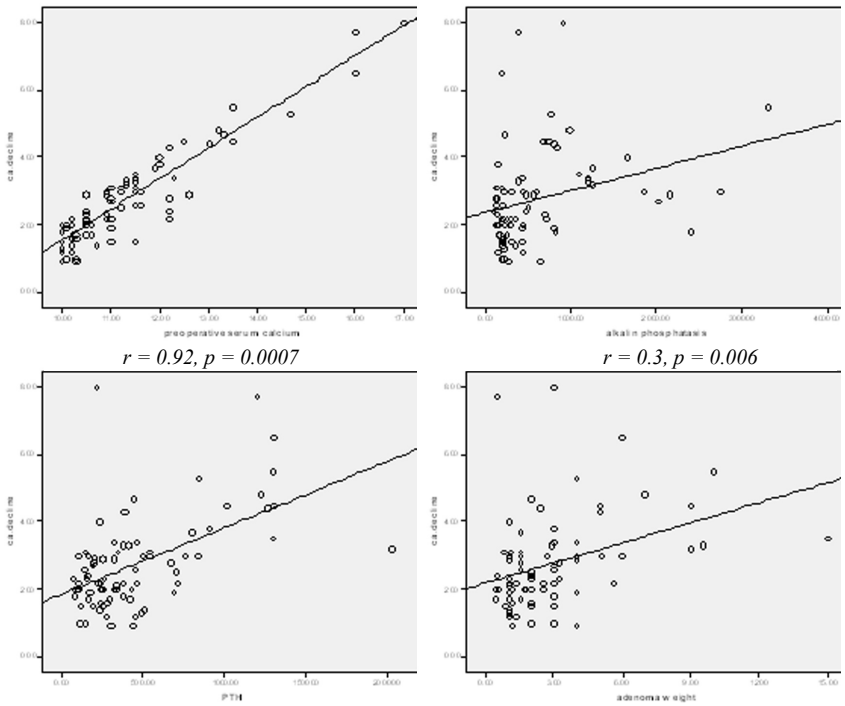


Fig. 1. Correlation between adenoma weight and preoperative PTH, serum calcium, alkaline phosphatase, and serum phosphate levels (P).



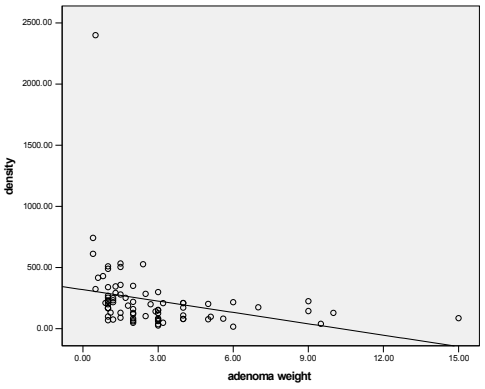
r = 0.92, p = 0.0007 *r = 0.3, p = 0.006*

r = 0.54, p = 0.0005 *r = 0.36, p = 0.001*

Fig. 2. Correlation between postoperative serum calcium decline and preoperative serum calcium, alkaline phosphatase and PTH levels, and adenoma weight.

Correlation between postoperative serum calcium and other parameters

There was a weak correlation between postoperative and preoperative serum calcium levels (r = 0.23, p = 0.03). Moreover, a non-significant negative correlation existed between postoperative serum calcium and adenoma weight (r= -0.17, p= 0.1), as well as preoperative ALP (r= -0.11, p= 0.3) and PTH levels (r= -0.11, p= 0.3). We formulated "calcium decline" as difference between postoperative and preoperative serum calcium levels. Serum calcium decline was correlated to adenoma weight (r=0.36, p=0.001), preoperative serum calcium (r=0.92, p=0.0007), PTH (r=0.54, p=0.0005) and ALP levels (r= 0.3, p=0.006) (Fig. 2). In multiple regression including preoperative serum calcium, ALP, PTH and adenoma weight, only preoperative serum calcium and PTH were correlated with postoperative serum calcium decline with p<0.001 and p=0.016 respectively.



R = -0.27, p = 0.01

Fig. 3.Correlation between adenoma weight and PTH/weight ratio (density).

As implied before, the ratio of serum PTH to weight of adenoma (PTH density) has been considered as an estimate of adenoma's function. As shown in Figure 3, we found a negative correlation between this ratio and adenoma weight (r= -0.27, p= 0.01). The ratio was significantly higher in adenomas lighter than 3 grams (p= 0.01). This implies that lighter adenomas may be more functional than heavier adenomas.

Discussion

Postoperative hypocalcemia after surgery for primary hyperparathyroidism has an incidence ranging from 0% in some published studies up to 30% in others [7]. Some sur-

geons routinely prescribe calcium supplementation to all patients after surgery for primary hyperparathyroidism. Therefore, these patients typically will have very few to no postoperative symptomatic hypocalcemia. Recently, surgeons have tried to define factors that could predict postoperative hypocalcemia and identify those patients who may need further monitoring or supplementation.

Correlation between serum PTH and adenomas weight has been studied by several authors [4-10], as well as serum calcium and adenoma weight [4,5,8,9]. However, results from different studies have been variable and even sometimes paradoxical. Rutledge et al [10] found a statistically significant but weak correlation (r= 0.16, Pearson's coefficient) between adenoma weight and preoperative calcium and PTH; while Dubost et al, [11] Wagner et al [12] and Randhawa et al [7] observed no relationship between serum calcium and PTH levels and adenoma weight or volume. A recent study on 63 single adenomas by Bindlish et al [4] demonstrated significant correlations between preoperative serum calcium and PTH and adenoma weight (p= 0.001). Likewise, Hedback et al [13] found a significant correlation ($p< 0.001$) between preoperative serum calcium and adenoma weight in 713 patients with single parathyroid gland disease operated on between 1956 and 1982.

Further studies examined the relationship between adenoma size, weight and postoperative hypocalcemia with conflicting results. Zamboni et al [14] reported a correlation between hypocalcemia and adenoma weight ($p<0.001$), but Strickland et al [15] found no statistically significant correlation between mean preoperative serum calcium, PTH and adenoma weight and postoperative serum calcium level, but no consensus has been reached. However, on contrary whether parathyroid weight alone can predict postoperative hypocalcemia. A study from the Oregon Health Sciences University in Portland correlated the slope of two postoperative calcium values drawn within 24 hours of surgery. They found that a negative slope with a decrease in calcium from the first draw to the second correlated with an increased risk of having hypocalcemia in the following days [16-22]. We did not graphically compare our postoperative calcium values, but this technique could be applied if one were to consistently draw at least two postoperative calcium values after surgery.

Here we provided our hypocalcemic patients with post-surgery calcium supplements. All the patients who initially developed postoperative hypocalcemia had already normal serum calcium levels by subsequent office visits several weeks later. This implies that long-term supplementation of calcium is not necessary, since any postoperative hypocalcemia after surgery for primary hyperparathyroidism seems to be transient.

We found a positive correlation between preoperative serum calcium, PTH and adenoma weight. In other words, higher preoperative serum calcium, PTH and ALP levels are in favor of heavier adenomas in primary hyperparathyroidism. We believe that the discrepancy between the results of our study and some of the previous literature is a result of excluding the patients with double adenoma and hyperplasia, as well as utilizing a relatively large sample size.

One may notice the very high levels of serum PTH and Adenoma weight when compared to serum calcium. Vitamin D deficiency can induce autonomous hyperparathyroidism either by increasing the amount of parathyroid tissue to such an extent that basal PTH secretion exceeded body needs (hyperplasia) or by facilitating growth of adenoma cells with spontaneous somatic mutations in the form of oncogene activation (PRAD1) or tumor suppressor gene inactivation (MEN1). This mechanism could explain the severity of PHPT in areas or populations with endemic vitamin D deficiency [17-20]. We searched local articles for similar data and found two articles stating that vitamin-D deficiency is already endemic in the region [18,19,21]. However, lack of data for vitamin-D in our database prevented us from confirming this deficiency in our patients.

Conclusion

Parathyroid adenoma weight was positively correlated with preoperative serum calcium, PTH, and ALP levels. These parameters could be used for predicting adenoma weight and size in patients with primary hyperparathyroidism. None of these parameters is reliable enough to predict postoperative serum calcium level. However, an estimation of postoperative calcium decline may be inferred by considering adenoma weight and preoperative serum levels of calcium, PTH, and ALP. Further studies are needed on correlation between postoperative calcium decline and hypocalcemic symptom to figure out whether to generally use prophylactic calcium supplements in postoperative patients.

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