Calcif Tissue Int (1992) 51:27–29

Calcified Tissue International

Normocalcemia with Persistent Increase of Parathyroid Hormone: A Prospective Study

H. Mulder,[1] W. H. J. Hackeng,[2] J. Koster,[1,*] and H. van der Schaar[3]

[1]Departments of Internal Medicine, [2]Endocrinological Biochemistry, and [3]Surgery, IJsselland Hospital, Prins Constantijnweg 2, Capelle a/d IJssel, The Netherlands

Received September 30, 1991, and in revised form December 20, 1991

Summary. Twelve patients were followed up for 3 months after parathyroidectomy. Serial measurements of serum parathyroid hormone (PTH), calcium, and phosphate were made. Four patients had an increased serum PTH postoperatively, which was already apparent by the third postoperative day. All patients became normocalcemic. Their hyperparathyroid-like phosphate parameters indicated that we were dealing with a biologically active PTH. Using preoperative biochemical parameters it was impossible to predict which patients would have an increased PTH post-parathyroidectomy (PTX). Probably the patients with high PTH post-PTX had higher parathyroid volumes. In our opinion after PTX, a normocalcemic high PTH situation should be avoided by 3½ parathyroid gland extirpation in all cases.

Operative treatment of primary hypercalcemic hyperparathyroidism (PHP) is usually followed by a normalization of serum calcium, lessening of symptoms, and a clinical "cure" that lasts for years. Most operative failures are obvious at the time of surgery, when no abnormal parathyroid tissue can be found. Persistence of recurrent hypercalcemia in the immediate postoperative period can be considered a sign of failure. Late recurrence of hypercalcemia after an initial successful parathyroidectomy is an infrequent phenomenon. Retrospective evaluation of parathyroid function after parathyroidectomy over a protracted period showed a continued hypersecretory state in many patients [1–4].

The purpose of this study was to evaluate prospectively the short- and long-term metabolic results of parathyroidectomy in a consecutive group of 12 patients.

Patients and Methods

Twelve hyperparathyroid patients (seven women, five men) entered the study. Mean age was 58 years (45–78 years). The diagnosis was based on increased serum calcium, increased serum parathyroid hormone (PTH), decreased serum phosphate (PO_4), decreased renal phosphate clearance ($TmPO_4/GFR$, (glomerular filtration rate)), and a normal or increased urinary calcium excretion. Twice before and 4, 8, and 24 hours; 3 and 7 days, and 3 months after parathyroidectomy (PTX) serum PTH, calcium, and phosphate were measured. Besides 3 months after PTX, the $TmPO_4/GFR$ was again calculated as follows:

$$\left(1 - \frac{\text{Cl } PO_4}{\text{Cl creatinine}}\right) \times \text{serum phosphate}$$

The concentrations of calcium, phosphate, alkaline phosphatase, and creatinine were measured using an autoanalyzer. PTH was measured radioimmunologically using the two-step hPTH (1–84) assay. The first step involved extraction and concentration of plasma PTH using solid phase antiamino-terminal PTH antibodies. After elution, the PTH immunoextract was analyzed using a sensitive mid- and C-region immunoassay [5]. A normal range of <4 pmol/liter 25 OHD was measured using a competitive protein binding assay, with a tritium tracer. The surgical procedure was standardized. At least four parathyroid glands were identified and the biggest one was extirpated. In the case of four glands of the same size, 3.5 glands were removed. The patients did not change their dietary calcium intake (with the exception of the direct postoperative period), nor were they using any medical treatment during the study period. For statistical analysis, Student's *t* test was used. The values are expressed as mean ± SD.

Results

All patients reached a normocalcemic state at the end, but there remained an increased serum PTH in four of them (group A). In the other eight patients, PTH was normalized (group B). Table 1 summarizes the preoperative biochemical data of the two groups of patients. Both groups of patients were alike in their biochemical profile, including their serum creatinine and 25 hydroxy vitamin D concentration. The initial, mean operative PTH levels of those patients whose later levels remained increased were 9.0 ± 2.6 pmol/liter compared with 8.5 ± 1.8 pmol/liter for those patients whose levels normalized postoperatively. The biochemical data on several measurements postoperatively for the two groups are reported in Table 2. In both groups, serum PTH levels during the first 24 hours post-PTX were undemonstrable. Three days post-PTX, the level of PTH was measurable in patients of group A. Thereafter, serum PTH was significantly higher in group A, but one must remember that this was the criterion for splitting the patients into two groups. However, 3 and 7 days post-PTX, a significant difference in serum PTH was already demonstrable. The serum calcium was higher 4 hours postoperatively in those patients who later had a persistantly increased PTH. On all other occasions serum calcium was not significantly different in the two groups. During the acute phase, serum phosphate was not different between the two groups; however, at the end of the study, 3 months post-PTX, the serum phosphate was lower in group A.

Serum creatinine and alkaline phosphatase did not significantly differ between the two groups, nor did serum creat-

* *Present address:* Internal Department, Dijkzigt Hospital, Rotterdam
Offprint requests to: H. Mulder

Table 1. Preoperative biochemical data of patients with increased serum PTH postoperatively (group A) and patients with a normalized serum PTH postoperatively (group B)

	No. patients	PTH (pmol/liter)	Serum Ca (mmol/liter)	Serum PO_4 (mmol/liter)	$TmPO_4$/GFR (mmol/liter)	Creatinine (μmol/liter)	Alkaline phosphatase (U/liter)	25 OHD (nmol/liter)
Group A	4	9.0 ± 2.6	2.98 ± 0.10	0.69 ± 0.22	0.54 ± 0.12	89 ± 11	84 ± 12	46 ± 12
Group B	8	8.5 ± 1.8	2.95 ± 0.08	0.72 ± 0.14	0.58 ± 0.09	94 ± 9	82 ± 6	43 ± 9

Mean values ± SD

Table 2. Biochemical data on several measurements before and after parathyroidectomy

	T_0	T_1	T_2	T_3	T_4	T_5	T_6
PTH							
Group A	9.0 ± 2.6	<0.8	<0.8	<0.8	2.8 ± 1.0[a]	3.1 ± 1.1[b]	7.5 ± 1.2[b]
Group B	8.5 ± 0.8	<0.8	<0.8	<0.8	<0.8	1.4 ± 0.9	2.0 ± 0.7
Serum Ca							
Group A	2.98 ± 0.10	2.34 ± 0.17[a]	2.19 ± 0.18	2.01 ± 0.19	1.88 ± 0.16	2.14 ± 0.11	2.29 ± 0.10
Group B	2.95 ± 0.08	2.18 ± 0.14	2.09 ± 0.18	2.00 ± 0.20	1.90 ± 0.19	2.18 ± 0.14	2.35 ± 0.12
Serum PO_4							
Group A	0.69 ± 0.22	0.99 ± 0.24	1.10 ± 0.28	1.44 ± 0.32	1.48 ± 0.22	1.02 ± 0.19	0.74 ± 0.15[a]
Group B	0.72 ± 0.14	0.89 ± 0.16	1.08 ± 0.20	1.29 ± 0.20	1.44 ± 0.28	1.06 ± 0.14	1.05 ± 0.09
$TmPO_4$/GFR							
Group A	0.54 ± 0.12						0.61 ± 0.05[b]
Group B	0.58 ± 0.09						1.01 ± 0.10
Creatinine							
Group A	89 ± 11						86 ± 10
Group B	94 ± 9						88 ± 14

Group A, not normalized PTH; group B, normalized PTH; mean values ± SD
T = time
[a] $P < 0.05$ group A vs group B
[b] $P < 0.01$ group A vs group B

inine change postoperatively. Thus, patients with persistently increased PTH had lower levels of serum phosphate 3 months post-PTX, as well as lower $TmPO_4$/GFR. All four patients of group A and four of eight patients in group B, called subgroup B1, were classified as having adenomata. Those patients classified as having parathyroid hyperplasia formed group BII. The biochemical differences between group BI and group BII are summarized in Table 3. PTH concentrations in the blood did not differ. Serum calcium tended to be higher and serum phosphate lower in the adenomata group.

Table 3. Biochemical data on several moments before and after parathyroidectomy in patient with normalized PTH

	T_0	T_1	T_2	T_3	T_4	T_5	T_6
PTH							
BI	8.4	<0.8	<0.8	<0.8	1.2	1.4	1.9
BII	8.7	<0.8	<0.8	<0.8	<0.8	1.3	2.1
Ca							
BI	2.98	2.29	2.16	2.03	1.89	2.17	2.37
BII	2.93	2.08	2.02	1.97	1.90	2.19	2.32
PO_4							
BI	0.70	0.85	1.06	1.23	1.41	1.06	1.04
BII	0.75	0.93	1.10	1.35	1.47	1.05	1.07
$TmPO_4$/GFR							
BI	0.60						0.99
BII	0.57						1.04

Group BI, adenoma; group BII, hyperplasia. Mean values ± SD

Discussion

As far as we know, this is the first study that follows PTH and other biochemical parameters before and after parathyroidectomy, in a prospective way. Four retrospective studies [1–4] included a total of 295 patients measuring serum PTH after PTX; 118 of these patients (40%) still had increased serum PTH levels. Three months postoperatively in our small group of patients, 4 of 12 (33%) had 3 months postoperatively increased serum PTH levels once more. Despite the extended PTH increment in such a large number of patients, all of them were postoperatively normocalcemic.

Is the post-PTX-measured PTH biologically inactive or are there effective adaptations that prevent overt hypercalcemia? It seems unlikely that the radioimmunoassay measures a biologically inactive part of the hormone, as four different groups using four separate iPTH assays documented this finding. Besides, as well as our retrospective study, this study demonstrated a lowered serum phosphate and $TmPO_4$/GFR, indicating a biologically active PTH. These data are not conclusive regarding inducing secondary effects or compensating mechanisms that could explain the normocalcemic state in patients with post-PTX-raised serum PTH levels. The slower decrease of serum calcium in the first hours postoperatively in patients classified as having adenomata compared with patients classified as hyperplasia could be explained by the operative procedure.

Hyperplasia surgery is more extensive (3.5 glands removed) compared with adoma surgery. The recovery of serum PTH is therefore much slower in the hyperplasia group,

as shown in Tables 2 and 3. The persistence of increased postoperative serum PTH in a substantial group of hyperparathyroid patients is in accordance with the concept of a metabolic cause of hyperparathyroidism rather than a true neoplastic cause. PTX does not attack the unknown stimulus causing hyperparathyroidism, but only diminishes the end organ of this stimulus. This non-neoplastic concept is further supported by DNA content research [6] (e.g., adenoma like DNA content in 29% of normal-sized parathyroid glands) and heterozygous X-linked isoenzyme marker research [7] (demonstrating a multicellular origin in parathyroid adenomata).

There seems to be a correlation between the existence of high post-PTX PTH levels and parathyroid volume. None of the patients with post-PTX-increased PTH had relatively small gland-tissue volume ("hyperplasia") in contrast with 50% of the "PTH cured" patients. Duh et al. [2] demonstrated more directly such a correlation. One can speculate on the following concept: The longer an unknown stimulus is operating, the more volume of parathyroid tissue is hyperfunctioning, and the greater the chance that PTX is not resulting in normalization of serum PTH. This concept does not explain the coexistent normocalcemic state.

This investigation demonstrates that a certain number of parathyroid glands are still producing a hypersecretion of biologically active PTH in the presence of normocalcemia and clinical cure of hypercalcemic symptoms. Whether or not the persistent increase of PTH postoperatively should be considered as a failure is an open question and needs further study. In our retrospective study, even 10 years post-PTX this group of patients were normocalcemic. In primary normocalcemic hyperparathyroidism, Purnell et al. [8] in a biochemical situation comparable with our post-PTX (high PTH, normocalcemic) subgroup, favors surgical intervention. The prognosis is better in those patients who underwent a parathyroidectomy (less hypertension, etc.). To diminish the chance, on second surgery of the neck, of persistent increase of PTH postoperatively, we would suggest performing a 3½ glandextirpation in all patients (including adenomata).

Acknowledgment: We thank Hanneke Dijkshoorn for technical assistance and Bob Morris for helping to prepare the manuscript.

References

1. Purnell DC, Scholz DA, Smith LH, Sizemore GW, Black BM, Goldsmith RS, Arnaud CD (1974) Treatment of primary hyperparathyroidism. Am J Med 56:800–809
2. Duh Q-Y, Arnaud CD, Levin KE, Clark OH (1986) Parathyroid hormone: before and after parathyroidectomy. Surgery 100: 1021–1030
3. Irvin GL, Newell DJ, Morgan SD (1987) Parathyroid metabolism after operative treatment of hypercalcemic (primary) hyperparathyroidism. Surgery 102:898–902
4. Schaar vd H, Koster J, Hackeng WHL, Mulder H (in press) Chirurgie van de bijschildklieren-waar doen we het eigenlijk voor? Ned.T.v. G
5. Hackeng WHL, Lips P, Netelenbos JC, Lips CJM (1986) Clinical implications of estimation of intact parathyroid hormone (PTH) versus total immunoreactive PTH in normal subjects and hyperparathyroid patients. J Clin Endocrinol Metab 63:447–453
6. Irvin GL, Bagwell CB (1979) Identification of histologically undetectable parathyroid hyperplasia by flow cytometry. Am J Surg 138:567–571
7. Fialkow PJ, Jackson CE, Block MA, Greenawald KA (1977) Multicellen origin of parathyroid "adenomas." N Engl J Med 297:696–698
8. Purnell DC, Scholtz DA (1981) Asymptomatic primary hyperparathyroidism. Mayo Clin Proc 56:473–479