World J. Surg. 28, 570–575, 2004
DOI: 10.1007/s00268-004-7124-y

WORLD
Journal of
SURGERY

Long-term Follow-up of Patients with Elevated PTH Levels following Successful Exploration for Primary Hyperparathyroidism

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Published Online: May 6, 2004

Abstract. Several studies have documented elevated parathyroid hormone (PTH) levels after seemingly successful exploration for primary hyperparathyroidism (pHPT). It is not known if this is a transient phenomenon after pHPT surgery or if it predisposes to recurrent disease. A series of 99 consecutive patients with pHPT who had solitary parathyroid adenomas were followed for 5 years. Serum levels of PTH and biochemical variables reflecting PTH activity were measured before operation, at 8 weeks postoperatively, and then yearly for 5 years. All patients were normocalcemic after exploration. At 8 weeks after operation 28% of the patients had elevated serum PTH levels; at 5 years this figure decreased to 16%. During the 5-year follow-up one group of patients normalized their PTH levels, another group's PTH levels fluctuated, and still another group had consistently normal PTH levels. Patients with fluctuating PTH levels had increased levels of serum calcium and phosphate. Some of these patients (15%) showed signs of impaired renal function. Two patients with consistently elevated PTH levels showed signs of mild renal dysfunction, and one of them developed recurrent HPT. Elevated PTH levels after successful parathyroid surgery is not a transient phenomenon. An increased risk for recurrent disease is postulated for some of the patients who do not normalize their PTH levels postoperatively, and long-term surveillance of these patients is suggested.

A significant number of patients with normocalcemia after surgery for a parathyroid adenoma have elevated levels of intact parathyroid hormone (PTH) at follow-up [1–6]. Currently, there is no consensus regarding the pathophysiology of this phenomenon. Several explanations have been suggested, such as persistent or recurrent primary hyperparathyroidism (pHPT), secondary HPT due to hypocalcemia, renal insufficiency, vitamin D deficiency, bone remineralization, and decreased peripheral PTH sensitivity [1–4].

It is not known if an elevated level of PTH after successful pHPT surgery is a transient or chronic phenomenon predisposing to recurrent pHPT. Therefore long-term follow-up of these patients is of great importance. The aim of the present study was to evaluate long-term changes in serum calcium and PTH levels as well as biochemical variables known to reflect PTH activity and renal function in patients with elevated serum PTH levels after successful pHPT surgery.

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Methods

Study Design

A series of 99 patients who had had a parathyroid adenoma removed were retrospectively divided into two groups: (1) those with postoperatively elevated serum PTH levels and (2) those with normal PTH levels after successful surgery for pHPT. Data were collected before surgery, 8 weeks after surgery, and thereafter yearly for 5 years and were added to a prospective database.

Patients

The study included 73 women and 26 men with a clinical and biochemical diagnosis of pHPT as well as a histologic diagnosis of parathyroid adenoma. The mean ± SD age of patients was 63 ± 13 years and the mean ± SD serum calcium level was 2.76 ± 0.19 mmol/L. The median weight of the excised parathyroid adenoma was 0.73 g (range 0.1–9.8 g). Two patients had slightly elevated serum creatinine levels (143 and 137 μmol/L, respectively). In a recent study, patients with a serum creatinine level below 160 mmol/L were considered to have pHPT [7]; our two patients therefore were assessed to have primary, not secondary, HPT. Altogether, 11 patients died during the follow-up period, and the mean ± SD age of these patients was 73 ± 8 years.

Clinical Variables

The medical history of each patient was recorded before surgery. None of the patients was preoperatively or postoperatively given supplements of calcium or vitamin D.

Surgery

All patients underwent neck exploration according to the principles of the unilateral approach [8]. Briefly, if an adenoma is found on the first side explored, it is excised. If the adenoma is not found on the first side or if the results of an intraoperative PTH measurement are inconclusive, comprehensive bilateral exploration is performed. In our cohort, 40 patients underwent unilateral and 59 bi-

lateral neck exploration. The skewed distribution of numbers between the two groups is due to a variety of localization procedures that were investigated during the study period.

Biochemistry

All blood samples were obtained after an overnight fast. Preoperative data were obtained from blood samples obtained the day before surgery. Serum ionized calcium concentrations were analyzed from blood samples normalized to pH 7.4 with an ion-selective electrode (ABL 505; Radiometer, Copenhagen, Denmark). Serum levels of intact parathyroid hormone (PTH) were measured using the N-tact intact PTH assay (Incstar, Stillwater, MN, USA). The sensitivity of this assay is 0.13 pmol/L. Serum concentrations of osteocalcin (bone gla protein) were measured with the commercially available Incstar Osteocalcin 125/RIA kit. High-performance liquid chromatography was used to determine the serum level of 25-hydroxyvitamin D_3 [s-25(OH)D_3], and 1,25-dihydroxyvitamin D_3 [s-1,25$(OH)_2D_3$] was measured with a radioreceptor assay (Incstar).

Serum levels of total calcium, creatinine, alkaline phosphatase activity, and phosphate were analyzed in a routine autoanalyzer (Kodak Ektachem 700xR-C; Eastman Kodak, Rochester, NY, USA). The glomerular filtration rate (GFR) was estimated by renal clearance of the contrast agent iohexol [9]. Using this method the average GFR for young, healthy subjects is 127 ml/min, with an expected reduction in subjects older than 55 years. Thus in 65-year-old patients the expected GFR would be about 80 ml/min.

Statistics

The results are expressed as the mean ± SD if not stated otherwise. For statistical evaluation of differences between groups, the Kruskall Wallis or Mann-Whitney U-test was used. For categorical data, statistical significance was analyzed by the χ^2 test and by Fisher's exact test when expected frequencies were less than five. The Friedman test followed by the Wilcoxon test was used for assessments repeated across time.

Results

All patients

Eight weeks after surgery all patients had normal or slightly low (below the reference value) serum calcium levels (2.33 ± 0.14 mmol/L).

The numbers of patients with elevated and normal PTH levels at 8 weeks and 5 years after operation, respectively, are shown in Figure 1. As can be seen, the follow-up data were complete for 73 patients. Altogether, 11 patients died during the 5-year follow-up: 7 patients after 1 year, 3 patients after 3 years, and 1 patient after 4 years. The cause of death in each case is not known, but all these patients suffered from cardiovascular disease preoperatively. Complete data for the 5-year follow-up were missing for 15 patients. During the 5-year follow-up the entire group of patients demonstrated significantly increased levels of calcium ($p < 0.05$), alkaline phosphatase ($p < 0.01$), phosphate ($p < 0.001$), and 25(OH)D_3 ($p < 0.01$) and a decreased level of 1,25$(OH)_2D_3$ ($p < 0.001$). There was a slight but insignificant decrease in the serum creatinine levels over the 5-year period.

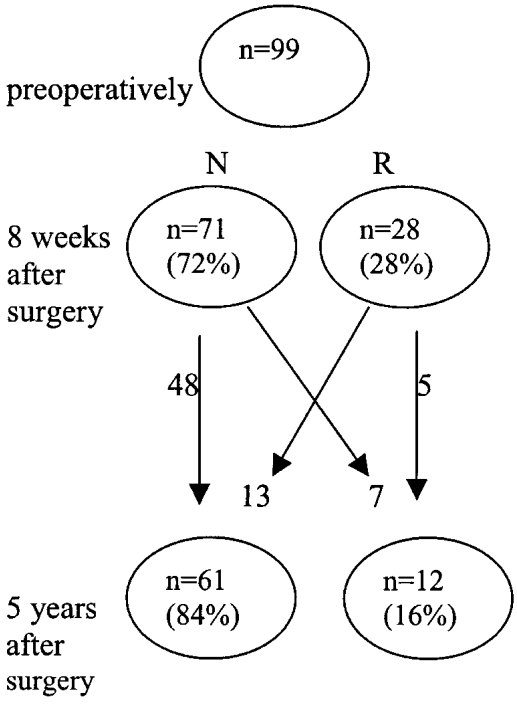

Fig. 1. Patients with elevated (R) and normal (N) serum levels of parathyroid hormone (PTH) 8 weeks and 5 years after surgery for parathyroid adenoma.

At 1 year after surgery 19 patients had elevated PTH levels (19%). At 5 years, 12 patients (16% of the investigated patients) had elevated PTH levels, and one of this group also had an elevated serum calcium level.

Patients with Normal and Elevated PTH Levels 8 Weeks Postoperatively

At 8 weeks after surgery, 28 patients (28%) had elevated PTH levels, and 71 patients (72%) had normal levels. The patients with elevated PTH levels had slightly lower serum total calcium levels (2.29 ± 0.11 mmol/L) than did the patients with normal PTH levels (2.35 ± 0.15 mmol/L) ($p = 0.052$).

There were no differences in age or gender between the patients with elevated PTH levels and those with normal PTH (62 ± 14 vs. 63 ± 13 years, $p = 0.97$). Furthermore, the two groups showed essentially the same clinical characteristics (data not shown). The preoperative biochemical data are shown in Table 1. The patients with postoperatively elevated serum PTH levels preoperatively had higher serum levels of PTH, alkaline phosphatase, and osteocalcin and lower levels of 25(OH)D_3. They also had larger adenomas. The mean weight of the parathyroid adenoma in patients with elevated PTH levels was 1.83 ± 2.03 g versus 0.90 ± 1.13 g in patients with normal PTH levels ($p < 0.01$). When comparing annual data during the 5-year follow-up, (Table 2), patients with elevated PTH levels at 8 weeks after surgery increased their calcium and phosphate levels and decreased their 1,25$(OH)_2D_3$ level.

At 5 years after surgery, the patients who had had elevated PTH levels at 9 weeks after surgery had lower serum 1,25$(OH)_2D_3$ levels (46 ± 18 vs. 58 ± 18 pmol/L, $p < 0.05$) and higher serum PTH levels (4.6 ± 1.8 vs. 4.0 ± 3.1 pmol/L, $p < 0.05$) than did patients with

Table 1. Preoperative biochemical data for patients with elevated or normal serum intact PTH 8 weeks after surgery for parathyroid adenoma.

Variable	Elevated PTH (n = 28)	Normal PTH (n = 71)	p*	Reference values
Total s-Ca (mmol/L)	2.82 ± 0.23	2.74 ± 0.17	0.19	2.20–2.60
s-PTH (pmol/L)	17.8 ± 17.3	10.0 ± 7.9	< 0.001	1.0–5.0
s-Phosphate (mmol/L)	0.89 ± 0.24	0.85 ± 0.15	0.84	0.70–1.60
s-Creatinine (μmol/L)	89 ± 45	81 ± 32	0.73	55–116
s-Osteocalcin (μg/L)	7.9 ± 4.2	5.1 ± 2.5	< 0.001	10–37
s-25(OH)D_3 (nmol/L)	40 ± 17	55 ± 17	< 0.001	20–100
s-1,25$(OH)_2D_3$ (pmol/L)	89 ± 10	89 ± 26	0.87	24–120
u-Ca (mmol/L)	4.8 ± 3.0	5.5 ± 3.5	0.29	2.5–8.0
s-ALP (μkat/L)	4.2 ± 1.5	3.4 ± 1.2	0.068	0.8–4.6
GFR (ml/min)	73 ± 29	81 ± 20	0.35	80–127

s: serum; u: urinary; PTH: parathyroid hormone; 25(OH)D_3: 25-hydroxyvitamin D_3; 1,25$(OH)_2D_3$: 1,25-dihydroxyvitamin D_3; ALP: alkaline phosphatase; GFR: glomerular filtration rate.

*The p value indicates the differences between groups.

Table 2. Annual postoperative biochemical data for the 28 patients operated on for parathyroid adenoma with elevated PTH levels 8 weeks after surgery.

Variable	Year 1	Year 2	Year 3	Year 4	Year 5	p*	Reference values
s-Ca (mmol/L)	2.32 ± 0.12	2.29 ± 0.12	2.28 ± 0.10	2.32 ± 0.10	2.35 ± 0.11	< 0.05	2.20–2.60
s-PTH (pmol/L)	5.0 ± 2.0	6.0 ± 5.1	5.2 ± 4.9	5.2 ± 4.8	4.6 ± 1.8	0.73	1.0–5.0
s-Phosphate (mmol/L)	1.08 ± 0.16	1.16 ± 0.13	1.13 ± 0.09	1.16 ± 0.13	1.22 ± 0.22	< 0.05	0.70–1.60
s- ALP (μkat/L)	3.1 ± 0.9	3.0 ± 0.8	3.2 ± 1.3	3.4 ± 0.9	3.1 ± 0.9	0.76	0.8–4.6
s-25(OH)D_3 (nmol/L)	53 ± 18	61 ± 20	59 ± 23	55 ± 19	57 ± 19	0.92	20–100
s-1,25$(OH)_2D_3$ (pmol/L)	62 ± 25	60 ± 15	54 ± 11	51 ± 17	47 ± 18	< 0.05	24–120
s-Creatinine (μmol/L)	110 ± 93	106 ± 87	88 ± 47	95 ± 67	116 ± 147	0.23	55–116

*The p value indicates changes over time.

normal PTH levels. No other differences in biochemical variables were found at this time.

Patients with Normal and Elevated PTH Levels 5 Years Postoperatively

At 5 years after surgery, 12 patients (16%) had elevated levels of PTH. Five of these patients had also elevated PTH levels at 8 weeks after surgery. Preoperatively, patients with elevated PTH levels at 5 years after surgery had higher PTH levels (23.3 ± 15.1 vs. 10.7 ± 10.5 pmol/L, $p < 0.005$) and higher adenoma weight (1.73 ± 1.52 vs. 1.09 ± 1.58 g, $p = 0.03$) than patients with normal PTH levels 5 years postoperatively. At the 5-year follow-up, patients with elevated levels PTH at 5 years after surgery had higher serum creatinine levels (156 ± 182 vs. 76 ± 15 μmol/L, $p < 0.01$) than patients with normal PTH levels. However, for patients with elevated or normal PTH levels 5 years after surgery, there were no differences in the levels of serum calcium (2.36 ± 0.15 vs. 2.31 ± 0.10 mmol/L, $p = 0.62$), urinary calcium (3.2 ± 2.5 vs. 2.8 ± 1.8 mmol/L, $p = 0.77$), or serum alkaline phosphatase (3.2 ± 1.0 vs. 3.0 ± 1.1 μkat/L, $p = 0.45$). There were also no differences in age or gender in patients with elevated or normal PTH levels at 5 years after surgery.

Patients with Normal, Normalized, or Variable PTH Levels during Follow-up

During the follow-up, 13 patients with elevated levels at 8 weeks after surgery had normalized PTH levels at the 1-year follow-up, and they remained normal thereafter (normalized group). In 40 patients (27 patients with normal PTH levels, 13 patients with elevated PTH levels 8 weeks after surgery), the PTH levels fluctuated between normal and elevated levels during the 5-year period (variable group). Another 44 patients had consistently normal PTH levels (normal group). Preoperatively, patients in the variable group had higher serum PTH levels (14.2 ± 15.7 vs. 8.9 ± 6.4 pmol/L, $p = 0.005$) and higher adenoma weight (1.56 ± 2.21 vs. 0.66 ± 0.43 g, $p = 0.01$) than patients in the normal group.

In the variable group, serum calcium ($p < 0.05$) and phosphate ($p < 0.05$) levels increased during the 5-year follow-up (Figs. 2a, c). In the normal group, there was an increase in serum PTH levels ($p < 0.05$) (Fig. 2b) and a decrease in serum 1,25$(OH)_2D_3$ levels ($p < 0.05$) (Fig. 2d). The normalized group showed an increase in serum 25(OH)D_3 levels ($p < 0.05$) (Fig. 2d) and a decrease in serum 1,25$(OH)_2D_3$ levels ($p < 0.05$) (Fig. 2e).

At the 5-year follow-up the three groups differed in their serum PTH and creatinine levels. The variable group had higher serum PTH (5.2 ± 4.0 vs. 3.1 ± 0.9 pmol/L, $p < 0.001$) and creatinine (88 ± 35 vs. 74 ± 13 μmol/L, $p < 0.05$) levels than the normal group and higher serum creatinine levels (88 ± 35 vs. 71 ± 11 μmol/L, $p < 0.05$) than the normalized group. The normalized group had higher serum PTH levels (3.9 ± 0.8 vs. 3.1 ± 0.9 pmol/L, $p < 0.001$) than the normal group.

Patients with Consistently Elevated PTH Levels

Two patients had consistently elevated PTH levels during the 5-year period. Both patients had signs of mild renal insufficiency with slightly elevated serum creatinine levels preoperatively and 5 years postoperatively. Both patients had a histologic diagnosis of a solitary parathyroid adenoma.

Patient 1 was a 67-year-old woman with hypertension and a

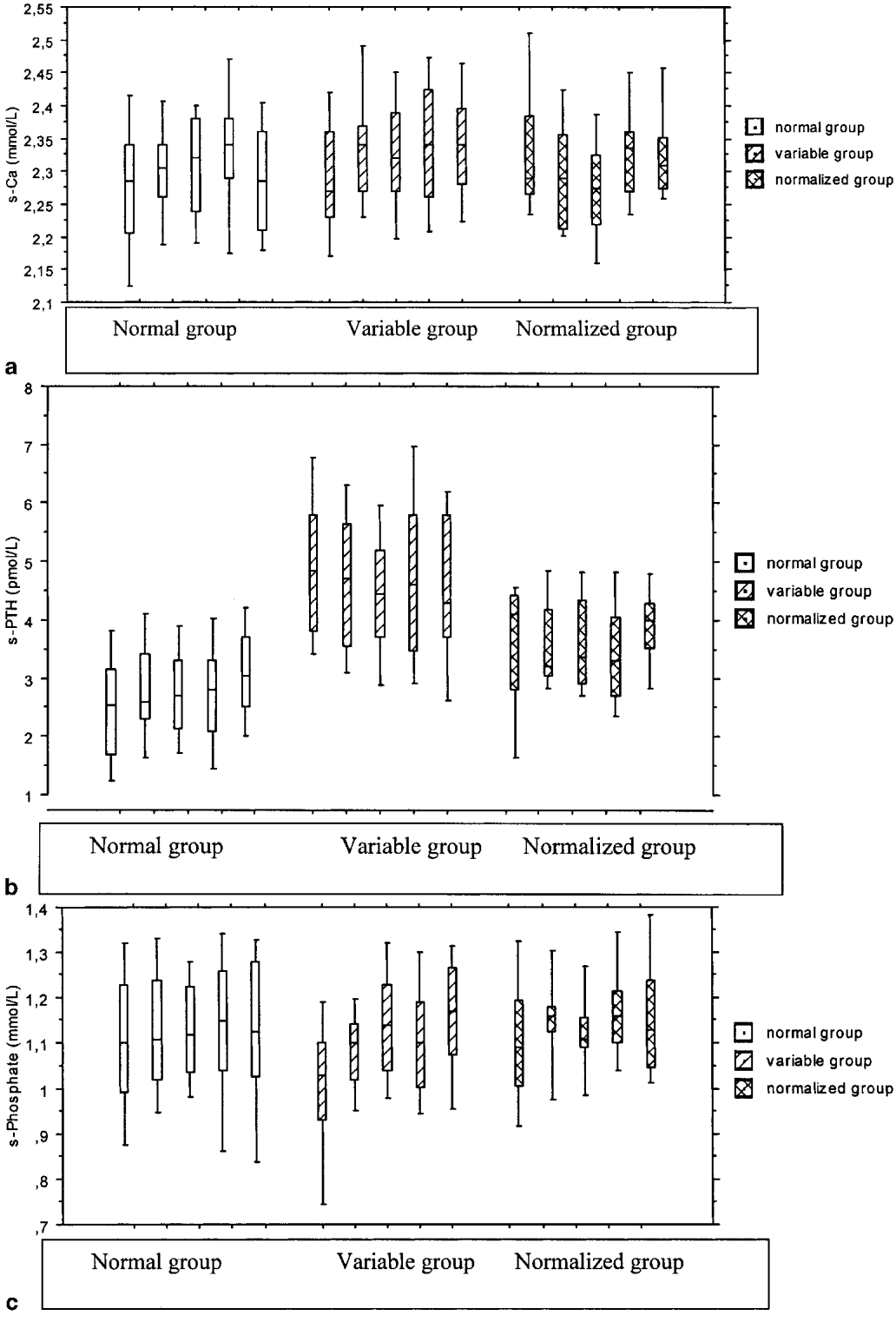

Fig. 2. Annual serum levels of calcium (**a**), PTH (**b**), phosphate (**c**), 1,25$(OH)_2$vitamin D_3 [$25(OH)_2D_3$] (**d**), and 25(OH)vitamin D_3 [$25(OH)D_3$] (**e**) for patients in the normal, variable, and normalized groups. Each group's five boxes indicate years 1, 2, 3, 4, and 5 after surgery, respectively. The box plot indicates median, upper, and lower quartiles and the extreme values. (continued on next page)

medical history of duodenal ulcer. She had a preoperative serum calcium level of 2.95 mmol/L (adenoma weight 1.67 g). Patient 2 was a 66-year-old woman with diabetes mellitus and cardiovascular disease. Her preoperative serum calcium level was 3.30 mmol/L (adenoma weight 5.40 g). Both patients had normal serum calcium levels 1 year after surgery (2.30 and 2.36 mmol/L, respectively). However, whereas patient 1 had a normal serum calcium level (2.36 mmol/L) at the 5-year follow-up, that of patient 2 was slightly elevated (2.65 mmol/L).

Discussion

In accordance with previous studies [1–6, 10–12] we have reported elevated serum PTH levels during the early period after surgery for

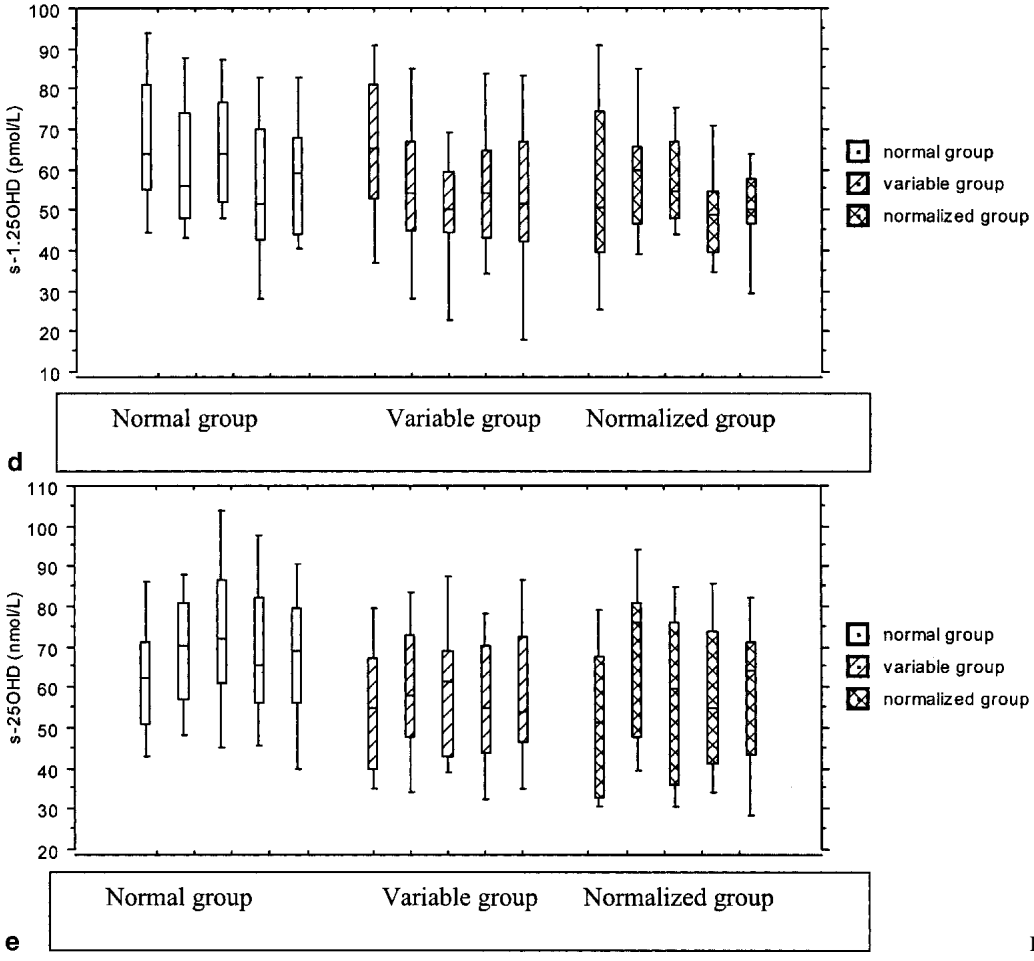

Fig. 2. *Continued.*

pHPT in about 30% of the patients. In contrast to another study [12], we showed that an elevated PTH level after surgery for parathyroid adenoma is not a transient phenomenon.

The pathogenesis behind a postoperative elevated intact PTH level after successful parathyroid adenoma surgery is not completely understood. At least during the early postoperative period (up to 1 year), the phenomenon has been shown to be associated with old age, advanced pHPT (high serum PTH levels, high adenoma weights), remineralization of cortical bone, decreased calcium absorption, and low levels of vitamin D_3 [2, 4, 12].

Although 12 patients (16%) had elevated PTH levels at 5 years, only 5 of the 12 had elevated PTH levels during the immediate postoperative period. Preoperatively, they had shown signs of more advanced pHPT disease with higher PTH levels and larger adenoma weights than the other patients. In contrast to the group with early postoperative elevated PTH levels, this late group was also characterized by a mild decrease in renal function.

We identified four subgroups of patients during the 5-year follow-up: patients with consistently normal PTH levels (normal group); patients with early elevated PTH levels that normalized during follow-up (normalized group); patients who demonstrated fluctuation between normal and elevated PTH levels (variable group); and patients with consistently elevated PTH levels.

Based on our data, it can be suggested that at least some of the patients who constitute the variable group have signs of impaired renal function. Because this group also had increased calcium and phosphate levels during the study period and had higher PTH levels at 5 years postoperatively, some of them may indeed run an increased risk of recurrent HPT secondary to decreased renal function. Interestingly, a recent study [13] showed that the overall recurrence rate of pHPT during a 10-year follow-up was about 5%, and 23% of the patients with recurrent disease had elevated serum creatinine levels.

On the other hand, one might speculate that elevated PTH levels during the immediate postoperative period found in the normalized group reflect low levels of vitamin D_3 and bone disease, with high bone turnover and postoperative remineralization. This group, however, still exhibited higher PTH levels than the normal group 5 years after surgery.

Only two patients had consistently elevated PTH levels during the entire study period. Both of these patients showed signs of mild renal dysfunction, and both had a histologically proven adenoma. One of these patients also had a serum calcium level 5 years after surgery suggestive of recurrent mild HPT. From a clinical point of view, it is interesting that of the 19 patients with increased PTH levels at 1 year after surgery recurrence was suspected in one patient (5%) 5 years postoperatively compared to none among the patients with a normal PTH level.

Conclusions

Elevated PTH levels after successful parathyroid surgery is not a transient but a dynamic phenomenon. Of the patients with elevated PTH levels 8 weeks after surgery, one group had normalized their PTH values by 1 year possibly due to decreased bone turnover. Other patients' PTH levels fluctuated between normal and elevated over time. These patients also had slightly increased serum calcium and phosphate levels. At least some of them showed signs of renal impairment. An increased risk of recurrent disease is postulated for this group of patients, and long-term surveillance is advised.

Résumé. Plusieurs études font état de la possibilité de taux élevés de parathormone (PTH) après intervention chirurgicale avec succès pour hyperparathyroïdie (pHPT). La question est de savoir s'il s'agit d'un phénomène transitoire après chirurgie pour pHPT ou une prédisposition à la récidive. Quatre-vingt neuf patients consécutifs, porteurs d'adénomes parathyroïdiens solitaires et de pHPT, ont été suivis pendant cinq ans. Les taux sériques de PTH et les variables biochimiques en rapport avec l'activité PTH ont été mesurés avant l'opération, huit semaines après l'intervention et ensuite, tous les ans, pendant cinq ans. Tous les patients étaient normocalcémiques après l'exploration chirurgicale. Huit semaines après intervention, 28% des patients avaient un taux élevé de PTH dans leur sérum; à cinq ans, ce chiffre était de 16%. Pendant le suivi de 5 ans, certains patients ont normalisé leurs taux de PTH, d'autres avaient un taux fluctuant alors qu'un troisième groupe avait des taux constamment normaux. Les patients qui avaient des taux fluctuants de PTH avaient également des taux élevés de calcémie et de phosphorémie. Parmi ces patients, 15% avaient des signes d'insuffisance rénale. Deux patients porteurs de taux élevés de PTH avaient des signes d'insuffisance rénale modérée et un a développé une récidive d'HPT. Un taux élevé de PTH après chirurgie apparemment satisfaisante sur la parathyroïde n'est pas un phénomène transitoire. Chez certains de ces patients qui ne normalisaient pas leurs taux de PTH en postopératoire, on peut postuler qu'ils sont à risque d'une récidive. Pour les patients ayant des taux élevés postopératoires, on préconise donc une surveillance à long terme.

Resumen. Diversos estudios han documentado niveles elevados de hormona paratiroidea (PTH) después de una aparentemente exitosa exploración por hiperparatiroidismo primario (pHPT). No se sabe si este es un fenómeno transitorio luego de cirugía por pHPT o una predisposición a enfermedad recurrente. Se realizó un seguimiento por cinco años de 99 pacientes consecutivos con pHPT por adenoma solitario. Se determinaron los niveles séricos de PTH y los parámetros bioquímicos de actividad de PTH con anterioridad a la operación, a las 8 semanas postoperatorias y luego anualmente por cinco años. Todos los pacientes aparecieron normocalcémicos después de la exploración. A las 8 semanas postoperatorias, 28% de los pacientes registraron elevación de los niveles séricos de PTH; a los 5 años esta cifra descendió a 16%. En el curso de los 5 años de seguimiento, un grupo demostró niveles normales de PTH, otro grupo demostró fluctuaciones y un tercer grupo demostró niveles normales constantes de PTH. Los pacientes con niveles fluctuantes de PTH incrementaron sus niveles de calcio y de fosfato. Algunos de ellos (15%) mostraron signos de función renal alterada. Dos pacientes con elevación constante de PTH demostraron signos de disfunción renal leve y uno de ellos desarrolló HPT recurrente. La elevación de los niveles de PTH luego de cirugía paratiroidea exitosa no es un fenómeno transitorio. En algunos de los pacientes en que no se normalizan los niveles de PTH en el postoperatorio, hay un riesgo mayor de enfermedad recurrente, por lo cual se sugiere seguimiento a largo plazo.

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