CLINICAL STUDY

Influence of renal function on clinico-pathological features of primary hyperparathyroidism

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Abstract

Objective: Disturbed renal function may play an important role in the clinico-pathological presentation of primary hyperparathyroidism (pHPT). We studied the influence of renal function on the clinico-pathological characteristics of 141 patients (123 women and 18 men) with surgically proven pHPT. **Methods:** The 141 patients were assigned to one of two groups based on creatinine clearance (C_{cr}) level: a renal insufficiency group ($n = 37$) in which C_{cr} of patients was < 70 ml/min and a normal renal function group ($n = 104$) in which C_{cr} was ≥ 70 ml/min. Clinical presentation and biochemical indices were evaluated and compared between the two groups.

Results: Age, and frequency of hypertension and of diabetes mellitus were significantly ($P < 0.001$, $P < 0.05$ and $P < 0.05$ respectively) higher in the renal insufficiency group than in the normal renal function group. Serum levels of calcium, intact parathyroid hormone and bone Gla protein were significantly ($P < 0.05$) higher and the excised parathyroid weighed significantly more ($P < 0.05$) in the renal insufficiency group than in the normal renal function group; however, serum 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) and 24 h urinary calcium excretion were significantly ($P < 0.001$ and $P < 0.05$ respectively) lower in the former than in the latter group. There was a significant inverse correlation between C_{cr} level and serum calcium ($r = 0.315$, $P < 0.001$) and a significant positive correlation between C_{cr} level, $1,25(OH)_2D$ ($r = 0.315$, $P < 0.001$), and 24 h calcium excretion ($r = 0.458$, $P < 0.0001$).

Conclusions: Clinico-pathological features of pHPT were notably influenced by even moderate renal insufficiency. Urinary calcium excretion decreased according to the decrease in glomerular filtration rate. Therefore, endocrinologists need to appraise urinary calcium excretion and renal function of pHPT patients when considering surgery or in discriminating familial hypocalciuric hypercalcemia.

European Journal of Endocrinology 148 597–602

Introduction

Primary hyperparathyroidism (pHPT) differs clinically from secondary HPT, which is a well-established complication of chronic renal failure. Parathyroid hormone (PTH) acts on the kidney to increase the production of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) (1), which increases intestinal absorption and renal reabsorption of calcium (2) and also aids calcemic action of PTH to the bone (3). In pHPT, $1,25(OH)_2D$ is increased by hypersecretion of PTH; conversely, lack of $1,25(OH)_2D$ can be a major factor in maintaining PTH hypersecretion in secondary HPT.

Prolonged hypercalcemia impairs renal function, and a reduced glomerular filtration rate (GFR) is a common finding in advanced-stage pHPT (4,5). There have been many studies on the metabolism of calcium, vitamin D and bone in both pHPT and secondary HPT; however,

there are few reports of the clinico-pathological effects of renal insufficiency in patients with pHPT. We have encountered several surgically proven pHPT patients in whom 24 h urinary calcium excretion was extremely low, probably due to renal insufficiency. Low urinary calcium excretion is the most significant discriminating factor between pHPT and familial hypocalciuric hypercalcemia (FHH). FHH is a dominantly inherited disorder of divalent cation metabolism, and there are clinical and biochemical overlaps with pHPT. However, surgery is not indicated for FHH.

We hypothesized that clinico-pathological features of pHPT are modified by impaired renal function, and we reviewed the clinico-pathological features of patients with surgically proven pHPT, giving special attention to renal function. This is important for the diagnosis and treatment of pHPT because impaired renal function is a well-known complication of pHPT (4, 5).

Patients and methods

Patient selection

One hundred and fifty-five patients with pHPT underwent surgery at our hospital between September 1998 and February 2002. There were none with renal failure. Of the 155 patients, we excluded three with multiple endocrine neoplasia type 1, one with parathyroid cancer and parathyroid apoplexy, one who was wheelchair-bound and three with persistent HPT after surgery. Creatinine clearance (C_{cr}) data were available for 141 of the remaining 146 patients, and these 141 were the study group. No patient had been taking medications that are known to interfere with calcium and vitamin D metabolism for at least 2 weeks before hospital admission. Of the 141 patients, 47 (33%) visited or were referred to us because of a thyroid nodule, and pHPT was diagnosed by calcium screening and a subsequent work-up including measurements of serum PTH and urinary calcium excretion. Medical histories included thyroidectomy for papillary thyroid cancer ($n = 7$), benign thyroid tumor ($n = 6$), and Graves' disease ($n = 2$). Two patients were referred for persistent hypercalcemia after parathyroidectomy.

Laboratory tests

Blood and urine samples were collected after overnight fasting. Serum levels of alkaline phosphatase, total calcium, albumin and inorganic phosphate were determined by routine automated procedures. Ionized calcium and magnesium concentrations were determined with an electrolyte analyzer (NOVA Biomedical, Waltham, MA, USA). The corrected calcium level was calculated as: (calcium concentration (mg/dl) + (4 - albumin (g/dl))). Serum intact PTH (iPTH) was measured by a two-site immunochemiluminometric assay. Serum 25-hydroxyvitamin D (25OHD) levels were measured by a competitive protein-binding assay with HPLC purification and had intra- and inter-assay coefficients of variation (CVs) of 5.8 and 12.6% respectively (6). Serum 1,25(OH)₂D levels were measured by a receptor-binding assay with bovine mammary gland receptor and had intra- and interassay CVs of 8.1 and 8.3% respectively (7). Serum bone Gla protein (BGP) was measured with a Mitsubishi Yuka BGP IRMA kit (Tokyo, Japan) that uses a mouse monoclonal antibody to human BGP. Urinary calcium excretion was assessed by atomic absorption spectrometry, and C_{cr} was calculated on the basis of ml/min per 1.48 m² of body surface area by measuring three consecutive urine collections at 24 h intervals while the patient was taking approximately 400 mg calcium/day. The normal value was assumed to be ≥ 70 ml/min(8). To assess bone resorption, an ELISA was used to measure urinary excretion of collagen

type 1 cross-linked N-telopeptides (NTx) (Osteomark; Ostex International, Seattle, WA, USA), and the results were corrected according to urinary creatinine concentrations assessed by a standard colorimetric method.

Statistical analysis

Mean $\pm$ S.D. data are shown unless otherwise indicated. ANOVA was used to assess differences between the groups. Multivariate analyses were done with a logistic model. Categorical data were analyzed with Pearson's χ^2 test. Correlation was determined by calculating Pearson's correlation coefficient. Statistical analyses were performed with SAS-JMP version 4.0.2 software (SAS Institute Inc., Cary, NC, USA). A two-sided $P < 0.05$ was considered significant.

Results

Patient's clinical and biochemical data are summarized in Table 1. Of the 123 women, 96 were postmenopausal, but none were under estrogen therapy. There was a history of nephrolithiasis in 35 patients, bone fracture in 15 and peptic ulcer in 13. Four patients complained of severe fatigue. The remaining 84 patients (60%) had asymptomatic pHPT. The mean serum calcium level was 2.70 ± 0.21 mmol/l. At least one enlarged parathyroid gland was resected in each patient; the mean weight of the resected parathyroid was 857 ± 1962 mg (range 66–21 834 mg). A single gland was diseased in 127 cases, and multiglandular disease was present in 14 cases.

The 141 patients were assigned to one of two groups based on C_{cr} level: a renal insufficiency group ($n = 37$)

Table 1 Preoperative clinical and biochemical data for pHPT patients. Mean $\pm$ S.D. data are shown.

	Value	Reference range
Age (years)	58 $\pm$ 13	—
Sex (F/M)	123/18	—
Serum albumin (g/l)	3.62 $\pm$ 0.29	3.5–4.8
Serum calcium (mmol/l)	2.70 $\pm$ 0.21	2.20–2.54
Ionized calcium (mmol/l)	1.48 $\pm$ 0.12	1.08–1.26
Serum corrected calcium (mmol/l)	2.80 $\pm$ 0.18	2.20–2.54
Serum phosphate (mmol/dl)	0.98 $\pm$ 0.16	0.81–1.45
Serum creatinine (μ mol/l)	62 $\pm$ 17	44–100
Serum blood urea nitrogen (mmol/l)	4.9 $\pm$ 1.4	3.2–6.8
Serum BGP (ng/ml)	18.4 $\pm$ 16.3	2.5–13
Serum alkaline phosphatase (IU/l)	136 $\pm$ 95	43–155
iPTH (pmol/l)	19 $\pm$ 30	1.1–7.4
25OHD (nmol/l)	35.8 $\pm$ 14.9	25–137
1,25(OH) ₂ D (pmol/l)	170 $\pm$ 65	48–144
Urinary NTx (nmol BCE/mmol creatinine)	167 $\pm$ 353	14–100
Parathyroid gland weight (mg) ^a	857 $\pm$ 1962	—

^a In the case of multiglandular disease, weight is calculated as the sum of resected parathyroid glands. BCE, bone collagen equivalents.

in which C_{cr} of patients was < 70 ml/min and a normal renal function group ($n = 104$) in which C_{cr} was ≥ 70 ml/min (8). Age and the frequency of hypertension, diabetes mellitus and multiglandular disease were significantly higher in the renal insufficiency group than in the normal renal function group (Table 2). Serum levels of calcium and iPTH, parathyroid gland weight and BGP were significantly higher in the renal insufficiency group than in the normal renal function group; however, 24 h urinary calcium and phosphate were significantly lower in the renal insufficiency group than in the normal function group (Tables 3 and 4). According to multivariate analysis of the clinical and biochemical factors, age- and serum-corrected calcium levels were significant

independent factors predictive of renal insufficiency (Table 5).

Correlations between C_{cr} and $1,25(OH)_2D$ and 24 h calcium excretion are shown in Fig. 1. In both groups, there was a significant correlation ($P < 0.005$) between C_{cr} and 24 h calcium excretion; however, a significant correlation between C_{cr} and $1,25(OH)_2D$ was found only in the renal insufficiency group ($P < 0.01$).

Discussion

Our study documents several clinico-pathological features of pHPT modified by renal insufficiency.

Table 2 Clinical data of pHPT patients per group. Mean $\pm$ s.d. data are shown.

	Renal insufficiency group ($n = 37$)	Normal renal function group ($n = 104$)	<i>P</i>
Age (years)	64 $\pm$ 11	55 $\pm$ 12	$< 0.001^a$
Sex (F/M)	30/7	93/11	0.192
Urinary stone disease (%)	27 (10 patients)	24 (25 patients)	0.718
Bone disease (%)	24 (9 patients)	20 (21 patients)	0.598
Hypertension (%)	46 (17 patients)	19 (20 patients)	< 0.005
Diabetes mellitus (%)	19 (7 patients)	7 (7 patients)	< 0.005
Parathyroid gland weight (mg) ^b	1450 $\pm$ 3586	646 $\pm$ 754	< 0.05
Single gland disease (%)	81 (30 patients)	93 (97 patients)	< 0.05
Multiglandular disease (%)	19 (7 patients)	7 (7 patients)	< 0.05

^a Statistical significance of between group difference determined by Student's *t*-test or Pearson's χ^2 test.

^b In case of multiglandular disease, weight is calculated as the sum of resected parathyroid glands.

Table 3 Biochemical data of pHPT patients per group. Mean $\pm$ s.d. data are shown.

	Renal insufficiency group ($n = 37$)	Normal renal function group ($n = 104$)	<i>P</i>
Serum albumin (g/l)	3.58 $\pm$ 0.35	3.63 $\pm$ 0.27	0.390 ^a
Serum calcium (mmol/l)	2.78 $\pm$ 0.26	2.68 $\pm$ 0.18	< 0.05
Ionized calcium (mmol/l)	1.53 $\pm$ 0.13	1.46 $\pm$ 0.11	< 0.005
Serum corrected calcium (mmol/l)	2.88 $\pm$ 0.23	2.77 $\pm$ 0.15	< 0.005
Serum phosphate (mmol/l)	0.95 $\pm$ 0.16	1.00 $\pm$ 0.16	0.116
Serum creatinine (μ mol/l)	75 $\pm$ 24	57 $\pm$ 11	< 0.001
Serum blood urea nitrogen (mmol/l)	5.7 $\pm$ 1.6	4.5 $\pm$ 1.1	< 0.001

^a Statistical significance of between group difference determined by Student's *t*-test.

Table 4 Clinical and biochemical data of pHPT patients per group. Mean $\pm$ s.d. data are shown.

	Renal insufficiency group ($n = 37$)	Normal renal function group ($n = 104$)	<i>P</i>
Serum BGP (ng/ml)	27.1 $\pm$ 28.5	15.8 $\pm$ 8.2	$< 0.005^a$
Serum alkaline phosphatase (IU/l)	158 $\pm$ 160	129 $\pm$ 55	0.104
iPTH (pmol/l)	28 $\pm$ 56	15 $\pm$ 9	< 0.05
25OHD (nmol/l)	37.7 $\pm$ 17.1	35.7 $\pm$ 13.9	0.498
1,25(OH) ₂ D (pmol/l)	145 $\pm$ 65	179 $\pm$ 63	< 0.01
Urinary NTx (nmol BCE/mmol creatinine)	223 $\pm$ 45	149 $\pm$ 315	0.306
24 h urinary calcium excretion (mmol)	5.07 $\pm$ 2.36	6.83 $\pm$ 2.10	< 0.001
Calcium excretion rate (%) ^b	2.14 $\pm$ 0.70	1.77 $\pm$ 0.51	< 0.005
24 h urinary phosphate excretion (mmol)	16.5 $\pm$ 4.6	20.9 $\pm$ 4.7	< 0.001
TRP (%)	81 $\pm$ 5	78 $\pm$ 7	< 0.05

^a Statistical significance of between group difference determined by Student's *t*-test.

^b Calcium excretion rate was calculated as: (urinary calcium (mg/dl) $\times$ serum creatinine (mg/dl)) / (urinary creatinine (mg/dl) $\times$ serum calcium (mg/dl)) $\times$ 100. TRP, tubular resorption of phosphate.

Table 5 Multivariate analysis of clinical and biochemical factors for renal insufficiency in patients with pHPT.

Clinical factor	P
Age	0.004
Frequency of hypertension	0.180
Frequency of diabetes mellitus	0.328
Frequency of multiglandular disease	0.085
Corrected calcium	0.013
Parathyroid weight	0.297

Figure 1 (A) Correlation between C_{cr} and 24 h urinary calcium excretion. ■, Renal insufficiency subjects; ○, normal renal function subjects. (B) Correlation between C_{cr} and serum $1,25(OH)_2D$. ■, Renal insufficiency subjects; ○, normal renal function subjects.

These have not been fully investigated previously, and they have important clinical implications for the diagnosis and treatment of pHPT. The degree of renal insufficiency in the present study was mild considering that the mean serum levels of creatinine and blood urea nitrogen in the renal insufficiency group were $75 \mu\text{mol/l}$ and 5.8 mmol/l respectively. There have been several studies documenting abnormalities in calcium, phosphorus and vitamin D metabolism in patients with renal disease. Secondary HPT is also present in moderate renal failure, and elevated blood levels of PTH have been found in patients with $C_{cr} < 70 \text{ ml/min}$ (9). Lucas *et al.* (10) noted a diminished mean concentration of $1,25(OH)_2D$ in nephrotic patients with a GFR of $50\text{--}90 \text{ ml/min}$ (mean 69.5). A C_{cr} of 70 ml/min was chosen to distinguish our two study groups because we hypothesized that the clinico-pathological features of pHPT may be influenced by secondary HPT.

Prolonged hypercalcemia impairs renal function, and a reduced GFR is common in advanced pHPT (4, 5). In our study, hypercalcemia was shown to be a significant risk factor for renal insufficiency. The incidence and severity of this renal impairment vary considerably among reports, probably due to both the heterogeneity of the patient samples studied and the different techniques used for estimating renal function. Several authors who monitored plasma creatinine levels in pHPT patients reported that renal function might remain normal despite long-standing hypercalcemia (11, 12).

The majority of our patients were asymptomatic; five (3.5%) had mildly elevated serum creatinine levels, and 37 (27.0%) had a $C_{cr} < 70 \text{ ml/min}$. The National Institutes of Health Consensus Development Conference recommends measurements of serum creatinine and C_{cr} and advises surgery if C_{cr} is reduced $> 30\%$ from that of age- and sex-matched controls (13). The current recommendation is unchanged, but determining C_{cr} is recommended only in the initial assessment of patients with pHPT because its determination is variable and often unreliable in the outpatient setting. Silverberg *et al.* (14) reported that the renal function of patients with asymptomatic pHPT followed up for 10 years did not decrease significantly; however, we should keep in mind that renal damage, once established, persists and may even progress after parathyroid adenectomy (15).

Hypertension has been reported to be more prevalent in pHPT patients than in matched control subjects (16). The frequency of hypertension was significantly higher in our renal insufficiency group than in our normal renal function group. This is expected because the former group was older than the latter group. Further, the prevalence and severity of hypertension increase as renal function declines, even in patients with serum creatinine levels within the normal range (17). Hypertension secondary to early-stage kidney disease

may be related to impaired sodium excretion, leading to an increase in blood volume and exchangeable body sodium (18). The frequency of diabetes mellitus was also significantly higher in the renal insufficiency group than in normal renal function group. There have been epidemiological studies showing overrepresentation of pHPT in diabetes mellitus and vice versa (19). Glucose intolerance and reduced peripheral insulin sensitivity have been shown in patients with pHPT (20). The high frequency of hypertension in pHPT patients together with peripheral insulin insensitivity may contribute to the increased risk of cardiovascular disease in these patients (21).

Whereas the majority of our patients had serum $1,25(\text{OH})_2\text{D}$ levels within the normal range, the mean level in the renal insufficiency group was significantly lower than that in the normal renal function group, although the former group had a higher PTH level than the latter group. PTH increases production of $1,25(\text{OH})_2\text{D}$ from 25OHD by stimulating renal $1\text{-}\alpha\text{-hydroxylase}$ activity (1), and the serum 25OHD level did not differ between our two groups. This observation is clinically important and key to understanding progression of pHPT, which can be caused by loss of renal mass and resistance to PTH in patients with renal dysfunction. There are several reports that serum $1,25(\text{OH})_2\text{D}$ concentrations start to decline early in the course of renal failure (10, 22, 23). Prolonged high circulating PTH concentrations induce downregulation of PTH peripheral receptors. Tomlinson *et al.* (24) showed that the urinary cAMP response to PTH is blunted in patients with HPT and that this phenomenon tends to occur in patients with high endogenous PTH concentrations. Because $1,25(\text{OH})_2\text{D}$ is required to correct skeletal resistance to the calcemic action of PTH (25), and it inhibits synthesis and secretion of PTH *in vitro* and *in vivo* (26, 27), reduced $1,25(\text{OH})_2\text{D}$ promotes proliferation of the parathyroid glands, resulting in a vicious cycle of HPT. We found an increased frequency of multiglandular disease in the renal insufficiency group. It can be assumed that renal insufficiency can lead to glandular hyperplasia.

Patients with pHPT have variably elevated urinary calcium levels, determined by the ratio between increased filtered load and enhanced calcium resorption. Hypocalciuria is the expected finding in normocalcemic patients with renal insufficiency, even when the GFR is minimally reduced. When the filtration rate falls to 25% or less, there is an increase in fractional calcium excretion that frequently parallels an increase in fractional sodium excretion (28). According to the NIH Consensus Development Conference statement (13), surgery is recommended if 24 h urinary calcium excretion is $>400\text{ mg}$ (9.9 mmol). Our study shows that 24 h urinary calcium excretion is significantly lower when renal function is insufficient than when renal function is normal; therefore, endocrinologists need to evaluate urinary calcium excretion when

considering renal function of patients for surgical indications or for diagnosing FHH.

Our study population differed slightly from that of other studies; there was a predominance of women and a higher prevalence of postmenopausal women than in other studies (14, 29). Because decreased renal function was mainly influenced by age and hypercalcemia, not by sex or menopause, and because the influence of moderate renal failure may not differ significantly between the two sexes, the main findings of this study can be applied to the general HPT population.

Clinico-pathological features of pHPT were notably influenced by even moderate renal insufficiency. Endocrinologists need to evaluate urinary calcium excretion and renal function of pHPT patients when considering surgery or discriminating between pHPT and FHH.

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Received 14 January 2003

Accepted 2 April 2003