The natural history of treated and untreated primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study

N. YU1, G.P. LEESE2, D. SMITH3 and P.T. DONNAN1

From the 1Dundee Epidemiology and Biostatistics Unit, Division of Clinical and Population Sciences and Education, 2Biomedical Research Institute, School of Medicine and 3Department of Surgery, University of Dundee, Dundee, Scotland, UK

Address correspondence to N. Yu, Dundee Epidemiology and Biostatistics Unit, Division of Clinical and population Sciences and Education, MacKenzie Building, Kirsty Semple Way, University of Dundee, Dundee, Scotland, DD2 4BF, UK. email: n.yu@cpse.dundee.ac.uk

Received 19 November 2010 and in revised form 22 December 2010

Summary

Background: Primary hyperparathyroidism (PHPT) is a common endocrine disorder with the majority of cases being mild and untreated.

Aim: To provide an update on the natural history of treated and untreated PHPT.

Design: Retrospective population-based observational study.

Methods: From 1997 to 2006, a well-defined cohort of PHPT patients was established in Tayside, Scotland. Subsequent cohorts of ‘mild untreated’ and ‘surgically treated’ PHPT patients were selected for the present study. Their serum calcium (S-Ca) and PTH concentrations were followed until September 2009. Surgical outcomes were evaluated using hospital admission data.

Results: A total of 904 ‘mild untreated’ patients were identified (median follow-up = 4.7 years), with a baseline median S-Ca of 2.62 mmol/l. A general decreased trend was observed in the S-Ca concentration for up to 12 years but an increasing trend in PTH (P < 0.001 in both instances). Disease progression, defined as an increase in S-Ca concentration, was observed in 121 patients (13.4%). Twenty-six (2.9%) patients had undergone surgery during the subsequent follow-up period. Baseline age and PTH concentration were the only significant risk factors for disease progression. In comparison, there were 200 ‘surgically treated’ patients (median follow-up = 5.8 years). S-Ca was normalised after surgery, in 196 patients (98%). Hospital admissions for renal complications were reduced after surgery. In conclusion, most untreated patients with mild PHPT had no progression of S-Ca but approximately 15% did show some evidence of progression. Parathyroidectomy, with a high success rate, normalised the S-Ca in patients with PHPT.

Introduction

Primary hyperparathyroidism (PHPT) is characterized by an elevated serum calcium (S-Ca) and plasma parathyroid hormone (PTH) concentrations, usually as a result of a single over-active parathyroid gland. With automated biochemical screenings becoming more routinely available, diagnosis is earlier and the majority of patients (>85%) are now asymptomatic. Although parathyroidectomy (PTX) is the only definite cure for the disease, conservative management has been favoured, as few complications have been observed among asymptomatic PHPT.1–8 Studies of the natural history of
asymptomatic PHPT have continued since the 1980s but the generalizability is limited, often due to small patient numbers. In light of the shift to a further subclinical profile of PHPT with absence of any traditional symptoms, the third international workshop was held in May 2008, with a focus on reviewing and updating the diagnosis and management of asymptomatic PHPT. In order to answer the question of whether or not asymptomatic PHPT patients could be left safely under surveillance without surgery, it was recommended that issues on disease progression, involvement of other complications and possible predictors of complications among mild asymptomatic PHPT patients, should be addressed.

Previously, in our region of Scotland, UK, a well-defined cohort of PHPT patients was established during the decade of 1997 to 2006. In a previous study, we have shown that this is a common disease with possibly 1% of the total population affected, and that there are increased risks of mortality and morbidity for CVD, cerebrovascular disease, cancer and other poor outcomes, in patients with mild PHPT. This present article is aimed at providing an update of the natural history, with a focus on S-Ca progression, of untreated PHPT patients with raised, but milder hypercalcaemia (S-Ca < 2.90 mmol/l at the baseline). Complete observational data at population level, including biochemical test results and hospital admissions, were linked to observe the long-term results in these patients and to compare the outcomes with those who had undergone PTX. We also proposed to look at the surgical cure rate and possible predictors of S-Ca progression in unoperated patients.

Patients and methods

Study population

During the period from January 1997 to December 2006, a pre-defined biochemical algorithm, in addition to other hospital data, was used to establish a data set of all patients with PHPT in Tayside, Scotland. Briefly, a positive biochemical diagnosis was made if a patient met either of the following criteria: (i) albumin-corrected S-Ca > 2.55 mmol/l (reference range 2.10–2.55 mmol/l) on at least two occasions, with plasma PTH concentration > 3 pmol/l (reference range 1.0–6.9 pmol/l) or (ii) albumin-correct S-Ca > 2.55 mmol/l on one occasion, with plasma PTH concentration > 6.9 pmol/l. Definite biochemical diagnoses were then confirmed using urine calcium excretion data (available in 30%), hospital data, including hospital admission data on PHPT, hospital operation and procedure data on PTX, nuclear medicine scans, renal function databases and hospital letters indicating positive PHPT and any additional PHPT cases were also added to the cohort. Further linkage to patient demographic information, inpatient hospital admissions, biochemical test results and community prescription from the Health Informatics Centre, was made possible via a unique anonymous patient identifier, the Community Health Index (CHI), in accordance with the Data Protection Act, to establish a complete and linked data set for all diagnosed PHPT patients.

By scrutinizing the linked data set, subsequent cohorts of ‘mild untreated’ and ‘surgically treated’ PHPT patients were selected to form the basis of the present study (Figure 1). The ‘mild untreated’ group were defined as untreated PHPT patients whose S-Ca concentrations were < 2.9 mmol/l within the first 6 months after a positive diagnosis with absence of previous (prior to PHPT diagnosis) fracture fragility, renal stones and renal failure and not treated with cinacalcet; the ‘surgically treated’ group were patients who had undergone PTX by the end of 2006. Further exclusion criteria were applied to the ‘mild untreated’ group. These were: (i) S-Ca was followed up for < 6 months; (ii) less than two S-Ca measurements within the first 6 months. For those who were biochemically identified PHPT patients, the date of first raised S-Ca (> 2.55 mmol/l) was treated as the date of PHPT diagnosis and the corresponding S-Ca was treated as the baseline value; for those who were identified solely from the hospital records, the result of S-Ca concentration tested on the date of admission was treated as the baseline value.

The study was approved by the Tayside Research Ethics Committee and the Tayside Caldicott Guardians.

Definition of disease progression

For the selected patients, all S-Ca test records after a positive PHPT diagnosis were compared to the baseline. If S-Ca increased by 0.2 mmol/l, or S-Ca reached 2.9 mmol/l during the study period, a marker was made indicating a biochemical progression of the disease.

Statistical methods

Descriptive statistics were used to summarize baseline characteristics of the patients. Differences in biochemical indices and follow-up times between sub-groups were tested using non-parametric methods because their distributions were non-Normal. Other differences were examined using independent-samples t-test or chi-squared test as
Changes in pooled biochemical indices were assessed using curve estimation. Within-subject changes in S-Ca and PTH concentrations during the follow-up period, in the ‘mild untreated’ group, were further estimated using linear mixed models, allowing repeated but unequal number of measurements within subjects. The Akaike’s information criterion (AIC) was used to select the best model in describing the trend. In addition, the Cox proportional hazards model was used to examine possible predictors of S-Ca progression. Predictor variables considered were baseline age, gender, baseline biochemical values and other pre-existing clinical complications. Each factor was tested individually, initially, to identify the most important predictors. In the ‘surgically treated’ group, the rates of developing other co-morbidities, or complications, denoted as number of events per five person years, before and after surgery were computed and compared using the Poisson Exact test. Co-morbidity information was obtained from the hospital admission records indicating an inpatient admission. Before surgery events included any admission from a positive PHPT diagnosis being made to the time of surgery; and post surgery events were any post-operative admission that occurred till the end of study. Rates of event were calculated as the number of event in each observed period divided by the total corresponding person time. Postoperative biochemical indices at 2, 6 and 12 months after surgery, were compared with the baseline. All statistical analyses were carried out using the SPSS (version 17) and SAS (Version 9.1) software, and statistical significance was demonstrated with \( P < 0.05 \).

**Results**

**Baseline characteristics**

During the decade of 1997 to 2006, we identified 1099 ‘mild untreated’ PHPT patients and 200 ‘surgically treated’ patients who were potentially eligible for this study (Figure 1). By examination of the biochemical records (consultant endocrinologist GL) of all the 1099 untreated patients, 195 patients were further excluded. These exclusions were made because of the following reasons: suppressed PTH concentration (<3 pmol/l) 6 months after a positive diagnosis \( (n=9) \); presence of low S-Ca concentration (<2.1 mmol/l) 6 months after a positive diagnosis \( (n=89) \) and PTH mediated hypercalcaemia was unclear in the remaining 97 patients. Thus, the final study cohort comprised 904 ‘mild untreated’ PHPT patients and 200 ‘surgically treated’ patients. The baseline characteristics of these patients are tabulated in Table 1. S-Ca was followed up from...
the date of PHPT diagnosis and was continued until
the end of September 2009 or death or migration
whichever was earlier, giving a median follow-up
of 4.7 years for the ‘mild untreated’ and 5.8 years
for the ‘surgically treated’ group, respectively.
‘Surgically treated’ patients were younger and with
higher baseline S-Ca and PTH concentrations than
the ‘mild untreated’ patients (P < 0.001 in all in-
stances; Table 1).

By the end of September 2009, there were 299
(33.1%) who had died in the ‘mild untreated’ group
and 28 (14.0%), in the ‘surgically treated’ group
(chi-square = 28.56, P < 0.001).

Surgical cure rate
S-Ca concentration was normalized after surgery
with median postoperative S-Ca concentration at
2 months being 2.44 mmol/l, significantly lower
than the baseline measurement (P < 0.001), and re-
mained stable within the normal range at 6 and
12 months check-up (2.42 and 2.36 mmol/l, respect-
ively). Four patients showed evidence of S-Ca pro-
gression 6 months after the surgery, indicating
a surgical failure rate of 2%. There was no
homogeneity among these four patients in terms of
baseline characteristics. PTH was reduced from a
median value of 12.5 pmol/l at the baseline to a
postoperative value of 6.4 pmol/l at 2 months but
there was no trend observed over time. There was
no significant change in other biochemical indices,
such as postoperative alkaline phosphatase and
serum creatinine concentrations, when compared
to the baseline. Surgery also significantly reduced
risks of developing renal complications, among in
PHPT patients (Table 2).

Disease progression among mild,
untreated PHPT patients
Of the 904 mild untreated patients, biochemical in-
dices were followed up over a maximum of 12-year
period. A total of 15 741 post-diagnosis measure-
ments of S-Ca were made. According to the AIC,
the linear mixed model adjusted for age as a time
dependent variable and gender provided the best fit
for both S-Ca and PTH concentrations, which
showed a decreasing trend in S-Ca by time and an
increasing trend in PTH (P < 0.001 in both in-
stances). Figure 2 illustrates changes in pooled
S-Ca and PTH concentrations by follow-up time.
The pooled median S-Ca concentration regressed
to normal range within the first year and remained
stable, with a significant decreasing trend (P < 0.001)
over a 10-year period of observation. The pooled
median PTH concentration, on the contrary, was
persistently above the upper limit of normal range
(6.9 pmol/l), with an increasing trend (P < 0.001).
Serum creatinine and alkaline phosphatase fluctu-
ated around the normal ranges, with no clear pat-
terns identified.

Over one tenth of the ‘mild untreated’ patients
(n=121, 13.4%) developed evidence of progres-
sion, with a mean time to progression of 3.2 years

Table 1 Baseline characteristics of patients with mild untreated PHPT and PHPT treated with surgery

<table>
<thead>
<tr>
<th>Variables</th>
<th>Mild untreated</th>
<th>Surgically treated</th>
<th>P-value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>904</td>
<td>200</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age, mean (SD) (years)</td>
<td>67.3 (13.5)</td>
<td>58.2 (13.9)</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>674 (74.6%)</td>
<td>151 (75.5%)</td>
<td>NS</td>
<td>–</td>
</tr>
<tr>
<td>S-Ca follow-up, median months (range)</td>
<td>56 (6.2–152.1)</td>
<td>70 (7.5–154.7)</td>
<td>&lt;0.001</td>
<td>–</td>
</tr>
<tr>
<td>Baseline biochemical indicesa</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mmol/l)</td>
<td>2.62 (2.55–2.89)</td>
<td>2.80 (2.56–5.49)</td>
<td>&lt;0.001</td>
<td>(2.1–2.55)</td>
</tr>
<tr>
<td>PTH (pmol/l)</td>
<td>6.5 (3.0–29.9)</td>
<td>12.7 (3.9–274.0)</td>
<td>&lt;0.001</td>
<td>(1.0–6.9)</td>
</tr>
<tr>
<td>Alkaline phosphatase (µ/l)</td>
<td>94 (28–1187)</td>
<td>91 (43–516)</td>
<td>NS</td>
<td>F (20–190) M (30–150)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>96 (56–150)</td>
<td>92 (48–1266)</td>
<td>NS</td>
<td>F(50–160) M (60–190)</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>5.10 (1.69–14.08)</td>
<td>5.23 (2.4–9.4)</td>
<td>NS</td>
<td>(ideal ≤ 5)</td>
</tr>
</tbody>
</table>

a Biochemical values and follow-up time are shown as median (range), as the nature of non-normal distribution, Serum calcium was corrected for albumin.

Table 2 Rates (event per 100 person years) of developing other co-morbidities before and after parathyroidectomy in the 200 surgically treated PHPT patients

<table>
<thead>
<tr>
<th>Other complications</th>
<th>Before surgery</th>
<th>After surgery</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>2.48</td>
<td>1.66</td>
<td>NS</td>
</tr>
<tr>
<td>Renal stones</td>
<td>3.10</td>
<td>0.38</td>
<td>0.01</td>
</tr>
<tr>
<td>Renal failure</td>
<td>4.96</td>
<td>0.90</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Osteoporosis fractures</td>
<td>1.56</td>
<td>0.76</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.86</td>
<td>2.30</td>
<td>NS</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>0.32</td>
<td>0.12</td>
<td>NS</td>
</tr>
</tbody>
</table>
Figure 2. Changes in biochemical indices (pooled median values) among mild untreated PHPT patients with error bar (vertical segments on the curve) representing 95% confidence intervals. The reference line indicating the upper limit of the normal reference. (a) Serum calcium concentration (upper limit of normal range = 2.55 mmol/l). (b) Plasma PTH concentration (upper limit of normal range = 6.9 pmol/l).
Patients who progressed were older, with longer follow-up and higher baseline S-Ca and PTH concentration than the un-progressed patients. According to the changes in individual’s S-Ca concentration, two types of progression were observed, these being ‘unsustained progression’ and ‘persistent progression’. Nine patients (1.0% of the total ‘mild untreated’ patients) had ‘persistent progression’, i.e. their S-Ca remained at a progressed level for more than a 6-month interval, with the last S-Ca concentration being progressed compared to the baseline. In the majority of patients (102, 84% of all progressed patients) who progressed, S-Ca concentration later decreased, defined as ‘unsustained progression’. Ten patients of the original 121 patients who progressed could not be grouped by progression type, due to insufficient follow-up time.

Twenty-six (2.9%) patients from the ‘mild’ initially ‘untreated’ group were eventually surgically treated during the follow-up period of 2007 to September 2009. Of these, nine had shown progression in S-Ca prior to surgery and the others had developed other surgical indications. These patients had higher baseline S-Ca and PTH concentrations compared to the remaining ‘mild untreated’ patients \( (P<0.001 \text{ and } P=0.07, \text{ respectively}) \). Both S-Ca and PTH concentrations were normalized after surgery.

### Predictors of disease progression

Age at diagnosis and baseline PTH were shown to be significant risk factors of S-Ca progression with HR of 1.18 and 1.35, respectively (Table 4). The risk of progression increased by 35% for each 5 pmol/l increase in the baseline PTH concentration \( (P=0.017) \) and the risk increased by 18% for each 5 years increase in age at diagnosis \( (P=0.020) \). Figure 3 illustrates the increased rate of S-Ca progression in the ‘mild untreated’ patients by the range (in quintile) of their baseline PTH concentration. In each PTH quintile, there was no difference in the baseline S-Ca concentration.

### Discussion

This study provided up-to-date information on the natural history of asymptomatic ‘mild’ PHPT patients with a long follow-up period, in terms of the biochemical progression of the disease; our data is based on a larger patient cohort when compared to previous studies.\(^2,7,11,24-26\) Our patient cohort was based on an unselected stable population from all residents in the region. It represents the Scottish population structure and is similar to the UK population, although with slightly fewer ethnic minorities. As the diagnosis of cases was based on electronic records and subject to biochemical measurements, undiagnosed cases were not detected in this study. However, because the diagnosis was based on biochemical features rather than clinical referral patterns, we identified a large number of patients with borderline raised serum calcium concentrations, from a population base. In addition, due to the nature of retrospective observational study design, a substantial proportion of patients were lost-to-follow-up or had incomplete biochemical measurements (Figure 2). Despite this, the numbers, as shown in Figure 2, were fairly robust for 3–4 years during which time there were significant trends, which continued later even when the data was less complete. Nevertheless, since we have access

### Table 3  Comparison of baseline characteristics between progressed and un-progressed mild untreated PHPT patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>No progression</th>
<th>Progression</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, n (%)</td>
<td>783 (86.6)</td>
<td>121 (13.4)</td>
<td>–</td>
</tr>
<tr>
<td>Age, mean (SD), years</td>
<td>66.9 (13.4)</td>
<td>69.7 (13.7)</td>
<td>0.032</td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>587 (75)</td>
<td>87 (71.9)</td>
<td>NS</td>
</tr>
<tr>
<td>Follow-up time, median months (range)</td>
<td>55 (6.2–151.9)</td>
<td>64 (7.4–152.1)</td>
<td>0.018</td>
</tr>
<tr>
<td>Progression time, median months (range)</td>
<td>–</td>
<td>39 (6.8–114.0)</td>
<td>–</td>
</tr>
<tr>
<td>Baseline biochemical indices*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Serum calcium (mmol/l)</td>
<td>2.61 (2.55–2.88)</td>
<td>2.63 (2.55–2.89)</td>
<td>0.036</td>
</tr>
<tr>
<td>2. PTH (pmol/l)</td>
<td>6.4 (3.0–29.9)</td>
<td>8.5 (3.0–25.6)</td>
<td>0.006</td>
</tr>
<tr>
<td>3. Alkaline phosphatize (µ/l)</td>
<td>93 (28–1187)</td>
<td>94 (36–258)</td>
<td>NS</td>
</tr>
<tr>
<td>4. Serum creatinine (µmol/l)</td>
<td>96 (56–150)</td>
<td>96 (60–150)</td>
<td>NS</td>
</tr>
<tr>
<td>5. Cholesterol (mmol/l)</td>
<td>5.1 (1.7–14.1)</td>
<td>5.4 (2.2–8.7)</td>
<td>NS</td>
</tr>
</tbody>
</table>

*Biochemical values are shown as median (range), as the natural of non-normal distribution, serum calcium was corrected for albumin. Any difference between progressed and un-progressed subgroups was compared using either the Independent Samples t-test or Mann–Whitney test as appropriate.
to an exhaustive population database of all laboratory records, the reason for non-follow-up was more likely linked to cases with normalized test results. As a result, the interpretation of our results on disease progression, i.e. abnormal biochemical values, was robust, thus overcoming the limitations of study design.

The ‘mild untreated’ group were largely identified biochemically, who had mild hypercalcaemia with normal renal function and absence of previous fracture fragility at the time of diagnosis supplemented with clinical examination of case notes for further exclusions, therefore they reflected the contemporary asymptomatic PHPT patients who were without any overt symptoms. The definition of S-Ca progression (increase in serum calcium of >0.2 mmol/l or reached 2.9 mmol/l), broadly followed the NIH guidelines, and represented a clinically important change in S-Ca and indicated a worsening of the disease.17,27–30 By our definition, we found three patterns of S-Ca development, these being (i) no progression, (ii) unsustained progression and (iii) persistent progression. In support of previous studies on the natural history of asymptomatic PHPT, the majority of our mild patients (86.6%) had stable or decreased S-Ca over the 10-years of follow up from initial diagnosis.7,11 However, 3% of ’mild untreated’ patients developed surgical indications and had undergone

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unadjusted</th>
<th>Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI</td>
<td>P-value</td>
</tr>
<tr>
<td>Age (+5 year)</td>
<td>1.16 (1.07–1.25)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female (vs. Male)</td>
<td>0.93 (0.63–1.39)</td>
<td>NS</td>
</tr>
<tr>
<td>Baseline biochemical indices</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTH (+5 pmol/l)</td>
<td>1.49 (1.19–1.87)</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine (+5 μmol/l)</td>
<td>0.98 (0.94–1.02)</td>
<td>NS</td>
</tr>
<tr>
<td>Alkaline phosphatase (+5 μ/l)</td>
<td>0.99 (0.98–1.01)</td>
<td>NS</td>
</tr>
<tr>
<td>Cholesterol (+1 mmo/l)</td>
<td>0.95 (0.78–1.14)</td>
<td>NS</td>
</tr>
<tr>
<td>Pre-existing conditions (yes vs. no)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>0.92 (0.57–1.51)</td>
<td>NS</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>0.87 (0.38–1.98)</td>
<td>NS</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.49 (0.18–1.33)</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer</td>
<td>0.78 (0.38–1.60)</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.09 (0.62–1.94)</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 4** The results from the unadjusted and adjusted Cox proportional hazards models looking at possible predictors of progression of S-Ca in the mild untreated PHPT patients

**Figure 3.** The progression rate of serum calcium (dotted line) among mild untreated PHPT patients arranged by the baseline PTH values with fitted trend line (straight line). The baseline PTH concentration was divided into five quintiles; the rate was calculated as the number of patients who had shown progression of S-Ca divided by the total number of patients in each quintile. \( R^2 \) indicates the closeness of the regression line vs. the actual rates.
PTX by the end of September 2009. We found the rates of S-Ca progression did not differ by the baseline S-Ca concentration, but was positively correlated with the baseline PTH concentration. PTH as a genuine predictor of progression was also demonstrated in the multiple regression when we took both baseline biochemical indices and pre-existing co-morbidities into consideration.

In many patients the S-Ca reverted to the normal range but continued with a raised serum PTH concentration. Many patients will have been diagnosed with PHPT when they were unwell with other conditions. It is likely that the serum calcium improved when the condition unmasking the PHPT was treated. It is also possible that some of these may have had vitamin D insufficiency but it seems unlikely that vitamin D insufficiency would have been the reason for a raised S-Ca or S-Ca within upper reference range at baseline. There was no seasonal bias in serum calcium measurements, which may have been expected if vitamin D insufficiency had contributed in a major way to S-Ca concentrations. We found that the number of measurements was roughly equally spread through the year with similar pooled median calcium concentrations. In addition, as all patients presented with raised calcium at diagnosis, we have also examined the number of diagnoses made in each calendar month and found the numbers were similar (data not shown). Therefore, our data suggested that the influence of vitamin D insufficiency on our biochemical results was minimal. However, it is interesting that vitamin D insufficiency may contribute to the increased morbidity observed in so called ‘mild’ PHPT.

In the 200 ‘surgically treated’ PHPT patients, we have detected a high surgical success rate (98%), comparable to other series.24,31–33 In agreement with existing evidence, we have shown that both S-Ca and PTH concentrations were normalized post-operatively.11,33–38 In a recent randomized study, Bollerslev et al.34 found that successful PTX normalized S-Ca and PTH concentrations but had no observable benefit on cardiovascular morbidity. We used hospital admission data to evaluate the impact of successful PTX on cardiovascular involvement, renal complications and neuropsychological complaints and found no significant improvement in cardiovascular risk, although we may not be powered to detect such a difference, since there was a non-statistical trend. Moreover, we were unable to detect any surgical benefits on psychiatric symptoms; this was possibly due to the fact that neuropsychological complications in mild PHPT patients were too subtle to result in hospital admission. Existing evidence showing neurocognitive improvements were often detected retrospectively, when asking patients to compare particular symptoms before and after the surgery.2,24,25,39–41 We found, however, the risks of developing renal stones and renal failure were significantly reduced after successful surgery (Table 2).

In summary, in most patients with mild asymptomatic PHPT serum calcium did not progress if left untreated but around one tenth of them did show some evidence of progression. High baseline PTH concentration was and increasing age were important predictors of progression.

Acknowledgements

We thank the Chief Scientist Office in Scotland for providing a grant to undertake this work. We also thank the Health Informatics Centre, University of Dundee, for managing and supporting anonymized data.

Funding

Chief Scientist Office, Scotland (CZH/4/395, 2007); previous funding includes GSK, Pfizer and Amgen (to P.T.D.) and Amgen (to G.P.L.).

Conflict of interest: None declared.

References


