Relationship between serum parathyroid hormone, serum calcium and arterial blood pressure in patients with primary hyperparathyroidism: results of a multivariate analysis

F Lumachi, M Ermani, G Luisetto, A Nardi, S M M Basso, V Camozzi and G Favia

Abstract

Objective: To evaluate the possible relationship between serum calcium, serum parathyroid hormone (PTH) levels and arterial blood pressure (BP) in patients with primary hyperparathyroidism (HPT).

Design: A retrospective population-based study.

Methods: Charts of 194 patients with proven primary HPT were reviewed, and the main clinical and biochemical data were recorded. There were 48 men (24.7%) and 146 women (75.3%), with a median age of 59 years (range 23–82 years). Patients who used antihypertensive drugs or hormone replacement therapy had been previously excluded. All patients underwent successful parathyroidectomy, and were cured of their disease.

Results: There were no differences (P = NS) between men and women in systolic (143.3±19.1 vs 145.4±17.1 mmHg) and diastolic (87.1±12.3 vs 88.4±9.9 mmHg) BP, and in the main biochemical parameters. A significant (P ≤ 0.01) correlation was found between (i) serum calcium and serum PTH levels (r = 0.39, F = 88.36), (ii) age and BP, both systolic (r = 0.61, F = 118.16) and diastolic (r = 0.48, F = 64.5), and (iii) body mass index (BMI) and BP (r = 0.45 and 0.36 respectively). There was no significant association of serum calcium levels with systolic (r = 0.0974, t = 1.3422, P = 0.18) or diastolic (r = 0.1117, t = 1.5409, P = 0.12) BP, and of serum PTH levels with systolic (r = −0.0349, t = −0.4783, P = 0.63) or diastolic (r = −0.0793, t = −1.0913, P = 0.28) BP. Multivariate analysis confirmed that none of the independent biochemical parameters significantly correlated with BP, both systolic and diastolic.

Conclusions: In patients with primary HPT there is no relationship between PTH, calcium and BP. Thus, in hyperparathyroid patients, BP should be considered as an independent variable, mainly related to age and BMI.

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Introduction

A relationship between primary hyperparathyroidism (HPT) and arterial hypertension has long been suspected, but no convincing studies are available to confirm this hypothesis. Since the prevalence of hypertension in patients with primary HPT is higher than in the general population, both serum calcium (s-calcium) and serum parathyroid hormone (s-PTH) levels could be related to arterial blood pressure (BP). The aim of this study was to analyze whether a correlation exists between BP values, both systolic and diastolic, and the main clinical and biochemical parameters in a population of patients with confirmed primary HPT who underwent successful parathyroidectomy (PTx).

Subjects and methods

Charts of 194 consecutive patients (48 men (24.7%) and 146 women (75.3%)) with confirmed primary HPT were reviewed. Patients with a history of myocardial infarction, angina, stroke, diabetes mellitus, and those who used hormone replacement therapy, had been previously excluded. Also, we excluded from this study 18 patients (median age 58 years, range 52–78) who were treated for hypertension because BP values, modified by treatment, can potentially affect the correlation analysis, and a period of wash-out from treatment was impossible in patients undergoing surgery the next day. Their main clinical and biochemical data did not differ significantly, according
to age, with respect to patients who did not use anti-
hypertensive drugs.

Sixty-seven of 194 patients (34.5%) were asympto-
matic, and two (1.0%) had multiple endocrine neo-
plasia type 1. According to the 1990 NIH Consensus
Conference suggestions the main criteria for surgery
in asymptomatic patients were a value of s-calcium
≥ 3.0 mmol/l, or decrease of bone mass to 2 S.D. less
than the mean for age- and sex-matched control per-
sons (1).

After patients had rested in the supine position for at
least 10 min (between 0800 and 0900 h) venous blood
was sampled, and measurements of serum creatinine
(s-creatinine), s-calcium and intact s-PTH (PTH(1-
84)) were obtained. S-PTH was measured using a
two-site chemiluminescent immunometric assay,
while s-calcium and s-creatinine were measured by
standard laboratory methods. Arterial BP was recorded
using an automatic device. Three recordings were
made at 2–3 min intervals the day before the oper-
ation, and both mean systolic and diastolic values
(mmHg) were recorded in a database of information.
BP was also recorded using the same modalities on
the last postoperative day, 2–5 days after PTx. Age,
body mass index (BMI) and the main clinical and
biochemical data are reported in Table 1. To better
evaluate the influence of age on the relationship
between s-PTH, s-calcium and BP the population was
divided into five age-groups, as shown on Table 2.

All patients underwent successful PTx, and were
cured of their disease. The reported data are expressed
as means±S.D. A two-tailed Student’s t-test for
unpaired data was used to compare means of grouped
data. ANOVA was used to evaluate the linear relation-
ship between pairs of variables. The regression results
were expressed using the standardized β coefficient
and the partial correlation coefficient (r) calculation.
Furthermore, a measure of collinearity was provided
by R², which is the proportion of the variability in x
that is explained by the other variables when x is the
dependent variable in a regression on the others x
values. The significant level was set at P < 0.01.

**Results**

There were no differences (P = NS) between men and
women in systolic (143.3±19.1 vs 145.4±17.1
mmHg) and diastolic (87.1±12.3 vs 88.4±9.9 mmHg)
BP, and in the main biochemical parameters such as
s-creatinine (79.8±34.8 vs 76.1±18.0 μmol/l),
s-calcium (3.06±0.46 vs 2.91±0.27 mmol/l), and
s-PTH (210.3±176.6 vs 181.3±146.6 ng/l). Women
were significantly (P < 0.01) older (59.6±11.6 vs
51.9±15.0 years) than men. In the overall population,
ANOVA showed a significant linear correlation
between age and BP, both systolic (r = 0.61, F = 118.16, P < 0.01) and diastolic (r = 0.48, F = 64.5, P < 0.01). Also, a positive correlation of
s-calcium with s-PTH levels (r = 0.38632, F = 33.68,
P < 0.01) was found. There was no correlation
between s-calcium and BP, and between s-PTH and
BP, both systolic and diastolic.

As shown on Table 2, s-calcium levels were lower
(P < 0.01) in older patients (Group 5 vs Groups 1, 2
and 3), while s-creatinine and s-PTH values did not
differ (P = NS) among the age-groups of patients. No
relationship (P = NS) between BP and s-calcium, and
between BP and s-PTH, was found in either age
group, although the r value was relatively higher

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference intervals</th>
<th>Mean ± S.D.</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>—</td>
<td>57.7±12.9</td>
<td>59</td>
<td>23–82</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>—</td>
<td>24.7±12.6</td>
<td>25.5</td>
<td>22.4–29.2</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>—</td>
<td>144.8±17.5</td>
<td>150</td>
<td>105–180</td>
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<tr>
<td>Diastolic BP (mmHg)</td>
<td>—</td>
<td>88.0±10.5</td>
<td>90</td>
<td>60–110</td>
</tr>
<tr>
<td>Creatinine (μmol/l)</td>
<td>53–97</td>
<td>81.9±25.3</td>
<td>78</td>
<td>28–109</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>1.9–2.6</td>
<td>2.95±0.33</td>
<td>2.83</td>
<td>2.62–4.60</td>
</tr>
<tr>
<td>PTH (ng/l)</td>
<td>10–55</td>
<td>188.4±154.5</td>
<td>140</td>
<td>60–990</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Parameter</th>
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<th>Mean ± S.D.</th>
<th>Median</th>
<th>Range</th>
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</thead>
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<tr>
<td>S-creatinine</td>
<td>—</td>
<td>14.6±9.8</td>
<td>15.0</td>
<td>72.6–9.2</td>
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<tr>
<td>S-calcium</td>
<td>83.4±14.8</td>
<td>3.04±0.34</td>
<td>199.5±155.6</td>
<td>120.0±9.4</td>
</tr>
<tr>
<td>S-PTH</td>
<td>188.4±154.5</td>
<td>72.6–9.2</td>
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<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (years)</th>
<th>No. patients (%)</th>
<th>S-creatinine (μmol/l)</th>
<th>S-calcium (mmol/l)</th>
<th>S-PTH (ng/l)</th>
<th>Systolic BP (mmHg)</th>
<th>Diastolic BP (mmHg)</th>
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<tbody>
<tr>
<td>1</td>
<td>23–39</td>
<td>19 (9.8%)</td>
<td>83.4±14.8</td>
<td>3.04±0.34</td>
<td>199.5±155.6</td>
<td>120.0±9.4</td>
<td>72.6–9.2</td>
</tr>
<tr>
<td>2</td>
<td>40–49</td>
<td>26 (13.4%)</td>
<td>73.8±24.4</td>
<td>2.98±0.33</td>
<td>199.7±140.5</td>
<td>137.1±13.1</td>
<td>79.5±10.9</td>
</tr>
<tr>
<td>3</td>
<td>50–59</td>
<td>56 (28.9%)</td>
<td>83.6±34.4</td>
<td>3.04±0.44</td>
<td>178.8±159.4</td>
<td>142.6±15.0</td>
<td>84.4±9.0</td>
</tr>
<tr>
<td>4</td>
<td>60–69</td>
<td>59 (30.4%)</td>
<td>82.3±20.7</td>
<td>2.92±0.26</td>
<td>175.1±127.6</td>
<td>146.3±14.8</td>
<td>87.4±8.4</td>
</tr>
<tr>
<td>5</td>
<td>&gt;69</td>
<td>34 (17.5%)</td>
<td>84.2±20.2</td>
<td>2.79±0.20</td>
<td>212.7±198.3</td>
<td>153.3±14.6</td>
<td>91.8±8.7</td>
</tr>
</tbody>
</table>
operative BP values, both systolic and $differ$ while s-creatinine, s-calcium and s-PTH levels did not from those obtained in the overall population.

Results of multivariate analysis for systolic and diastolic BP in the overall population.

<table>
<thead>
<tr>
<th>Blood pressure (mmHg)</th>
<th>Patients</th>
<th>Age (years)</th>
<th>S-creatinine (µmol/l)</th>
<th>S-calcium (mmol/l)</th>
<th>S-PTH (ng/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 160</td>
<td>25</td>
<td>12.9</td>
<td>68.9±7.6</td>
<td>2.96±0.34</td>
<td>187.5±155.4</td>
</tr>
<tr>
<td>≤ 160</td>
<td>169</td>
<td>87.1</td>
<td>56.1±12.8</td>
<td>2.96±0.42</td>
<td>225.3±213.4</td>
</tr>
<tr>
<td>P</td>
<td>—</td>
<td>—</td>
<td>0.00</td>
<td>0.29</td>
<td>0.39</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 90</td>
<td>69</td>
<td>35.6</td>
<td>64.2±10.6</td>
<td>2.98±0.43</td>
<td>207.9±192.5</td>
</tr>
<tr>
<td>≤ 90</td>
<td>125</td>
<td>64.4</td>
<td>54.3±12.9</td>
<td>2.94±31.3</td>
<td>183.9±146.7</td>
</tr>
<tr>
<td>P</td>
<td>—</td>
<td>—</td>
<td>0.00</td>
<td>0.08</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Patients with systolic BP > 160 mmHg and diastolic BP > 90 mmHg were significantly ($P < 0.01$) older, while s-creatinine, s-calcium and s-PTH levels did not differ ($P = NS$) between the subgroups of hypertensive and normotensive patients (Table 3). Multivariate analysis showed that no independent biochemical parameters correlated with BP, and confirmed the linear correlation between BP, both systolic and diastolic, age and BMI (Table 4). Lower BP values were recorded in younger patients (< 50 years) with higher calcium and PTH levels; this subgroup represented less than a quarter of the total. Since age is a major determinant of BP and the mean age of the whole group is 60 years, the relationship between s-PTH, s-calcium and BP was assessed in subgroups of patients aged < 50 and ≥ 50 years (Table 5). The results did not differ from those obtained in the overall population.

Discussion

Primary HPT represents the most common cause of hypercalcemia, and its estimated age-adjusted incidence is 42 per 100 000 (2). Arterial hypertension is common in patients with primary HPT with reported rates ranging between 10 and 40%, and an average being about 30% (3). In 1982 Nainby-Luxemore et al. (4) compared the frequency of hypertension in a group of 124 patients with primary HPT with that found in cases matched for age and conditions considered of comparable surgical magnitude. The rate of hypertension was significantly ($P < 0.01$) higher (73 vs 43%), but the BP elevation was modest. Possible mechanism which have been postulated for the supposed hypertension include the direct effect of calcium and PTH and the consequences of renal damage produced by the hypercalcemia. Udén et al. (5), reporting clinical and biochemical data concerning 250 patients with primary HPT, found that the rate of hypertension was significantly higher (47 vs 28%), in patients older than 60 with respect to younger patients. However, since 60–70% of the patients with primary HPT were over 60 years of age, different causes of hypertension should be investigated, as BP is strongly related to age (1, 5, 6). In the present series, 35% of the patients

Table 4 Results of multivariate analysis for systolic and diastolic BP in the overall population.

<table>
<thead>
<tr>
<th></th>
<th>β</th>
<th>r</th>
<th>$R^2$</th>
<th>$t$</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.637175</td>
<td>0.614035</td>
<td>0.139471</td>
<td>10.6669</td>
<td>0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.473122</td>
<td>0.454172</td>
<td>0.082453</td>
<td>6.49521</td>
<td>0.0001</td>
</tr>
<tr>
<td>S-creatinine (µmol/l)</td>
<td>0.141095</td>
<td>0.154018</td>
<td>0.295462</td>
<td>2.13729</td>
<td>0.03</td>
</tr>
<tr>
<td>S-calcium (mmol/l)</td>
<td>0.085547</td>
<td>0.097427</td>
<td>0.244135</td>
<td>1.34223</td>
<td>0.18</td>
</tr>
<tr>
<td>S-PTH (ng/l)</td>
<td>−0.029155</td>
<td>−0.034863</td>
<td>0.173642</td>
<td>−0.47830</td>
<td>0.63</td>
</tr>
<tr>
<td>Diastolic BP</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>0.500002</td>
<td>0.481275</td>
<td>0.139471</td>
<td>7.52810</td>
<td>0</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>0.382214</td>
<td>0.361471</td>
<td>0.082453</td>
<td>5.97311</td>
<td>0.002</td>
</tr>
<tr>
<td>S-creatinine (µmol/l)</td>
<td>0.159169</td>
<td>0.155933</td>
<td>1.295462</td>
<td>2.16452</td>
<td>0.03</td>
</tr>
<tr>
<td>S-calcium (mmol/l)</td>
<td>0.109398</td>
<td>0.111681</td>
<td>0.244135</td>
<td>1.54093</td>
<td>0.12</td>
</tr>
<tr>
<td>S-PTH (ng/l)</td>
<td>−0.074098</td>
<td>−0.079340</td>
<td>1.173642</td>
<td>−1.09129</td>
<td>0.28</td>
</tr>
</tbody>
</table>
had diastolic BP > 90 mmHg. This finding can more likely be due to the inclusion of hypertensive patients not treated, but could also be ascribed to the preoperative stress, although the mean short-term postoperative BP did not differ (P = NS) from preoperative BP. BMI is a known determinant of BP. It has been shown that a BMI ≥ 25 was associated with substantially higher BP, and a gain of 1.25–1.7 kg/m² in BMI may correspond to an elevation of 1 mmHg in BP, in some studies (7, 8). No data are available regarding possible connections between primary HPT and BMI.

PTH is an important regulator of calcium homeostasis, involving bone and kidney. A direct relationship between PTH and hypertension has also been hypothesized, and a positive association of calcemia with PTH in patients with primary HPT is well known (9–11). In healthy human subjects chronic infusion of PTH has been shown to result in increasing BP levels, and moreover a co-action of PTH and PTH hypertensive factors have also been suggested in experimental studies (12–14). Several recent clinical studies report that in hypertensive patients calcium metabolism is altered, and PTH levels are frequently increased (14–16). In fact, calcitropic hormones, such as PTH and calcitriol, have been shown to be increased in some forms of hypertension. St John et al. (16), in a group of hypertensive elderly subjects, showed that PTH was an independent significant predictor of mean BP. Moreover, PTH levels, which are elevated both in patients with HPT and in those with essential hypertension, can probably influence intracellular calcium levels and subsequently smooth muscle contraction (17). Significant relationships were also found between cytosolic free calcium and magnesium and BP, independent of age (18). Although intracellular calcium may play a role in the genesis of essential hypertension facilitating vascular smooth muscle contraction, no correlation between BP and intracellular calcium in patients with primary HPT was found (19).

Hunt et al. (20) in a group of healthy normotensive individuals found that there was no linear correlation of BP with plasma ionized calcium. However, a significant inverse correlation between ionized calcium and BP in patients with low renin levels was observed. More recently, Jorde et al. (21), in a population of 946 unselected patients who were living in Norway, confirmed a linear correlation between age and BP, but no association between BP and s-calcium was found. In women with elevated PTH levels due to causes other than HPT, both systolic and diastolic BP were higher (P < 0.01) than in those with normal PTH levels, and patients with hypertension had s-PTH levels significantly higher than the normotensive (21, 22). We did not find such difference between male and female patients with primary HPT, in spite of the women being older than the men.

In a group of 583 elderly patients untreated for hypertension and who did not suffer from primary HPT, calcium and PTH levels significantly correlated with mean BP, and PTH correlated positively with age (16). Similar results were obtained in patients with essential hypertension, confirming the presence of alteration of calcium metabolism in those patients (20). Finally, the relationships between age, PTH and BP have also been investigated in normotensive patients by Brickman et al. (23), who found a significant correlation between PTH and both systolic and diastolic BP. Multivariate analysis showed that PTH maintained significant correlation with mean arterial BP.

Few studies consider the possible relationship between BP, calcium and PTH in patients with primary HPT, who typically are hypercalcemic with elevated s-PTH levels. It may probably be justified by the known chemical heterogeneity of hypertension in
patients with primary HPT, since both low and high renin activity values were observed in different primary hyperparathyroid hypertensive subjects (20). In a group of 441 patients with primary HPT studied by Lind et al. (24) the preoperative systolic BP was significantly ($P < 0.05$) correlated with s-calcium only when the influence of age was not considered. Therefore, they concluded that there is no simple cause-and-effect relationship accounting for hypertension in primary HPT. In our series both systolic and diastolic BP were related exclusively to age and BMI, and there was no correlation between BP and the main biochemical parameters. Sancho et al. (25) found that 12 of 56 patients (21.8%) with HPT were hypertensive, but the clinical and biochemical parameters that were considered did not differ significantly ($P = NS$) between the subgroups of normotensive and hypertensive patients. Similar results were described by Ude´n et al. (5) for patients > 60 years and < 60 years.

In conclusion, in patients with primary HPT the hypothesized correlation between s-calcium and BP, and between s-PTH and BP does not seem to exist, and thus in such patients arterial BP should be considered as an independent variable, mainly related to age.

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