Hyperparathyroidism in Patients with Primary Aldosteronism: Cross-Sectional and Interventional Data from the GECOH Study

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Context: Experimental studies suggest that aldosterone induces hypercalciuria and might contribute to hyperparathyroidism.

Objective: We aimed to test for differences in PTH levels and parameters of calcium and vitamin D metabolism in patients with primary aldosteronism (PA) compared with patients with essential hypertension (EH) and to evaluate the impact of PA treatment on these laboratory values.

Design, Setting, and Participants: The Graz Endocrine Causes of Hypertension study includes hypertensive patients referred for screening for endocrine hypertension at a tertiary care center in Graz, Austria.

Main Outcome Measures: Differences in PTH levels between patients with PA and EH.

Results: Among 192 patients, we identified 10 patients with PA and 182 with EH. PTH levels (mean ± sd in picograms per milliliter) were significantly higher in PA patients compared with EH (67.8 ± 26.9 vs. 46.5 ± 20.9; P = 0.002). After treatment of PA with either adrenal surgery (n = 5) or mineralocorticoid receptor antagonists (n = 5), PTH concentrations decreased to 43.9 ± 14.9 (P = 0.023). Serum 25-hydroxyvitamin D concentrations were similar in both groups. Compared with EH, serum calcium concentrations were significantly lower (2.35 ± 0.10 vs. 2.26 ± 0.10 mmol/liter; P = 0.013), and there was a nonsignificant trend toward an increased spot urine calcium to creatinine ratio in PA [median (interquartile range) 0.19 (0.11–0.31) vs. 0.33 (0.12–0.53); P = 0.094].

Conclusions: Our results suggest that PA contributes to secondary hyperparathyroidism. Further studies are warranted to evaluate whether PTH has implications for PA diagnostics and whether mineralocorticoid receptor antagonists have a general impact on PTH and calcium metabolism.

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Primary aldosteronism (PA) is associated with an excess cardiovascular morbidity and mortality risk that cannot be explained by arterial hypertension alone (1). Hence, aldosterone excess may exert deleterious effects beyond blood pressure regulation. Apart from various harmful aldosterone effects on heart and vessels, evidence exists that aldosterone may also impact on mineral homeostasis by increasing renal and fecal loss of calcium and magnesium (2–5). This in turn may stimulate the secretion of PTH. Elevated PTH is, beyond its well-known effects on bone and calcium metabolism, also considered a cardiovascular risk factor (6, 7). In this context, experimental studies in rats have shown that aldosterone excess is accompanied by secondary hyperparathyroidism that is reversible by mineralocorticoid receptor (MR) antagonist therapy (2, 3). Human data on this topic are sparse, but we and others have previously shown significant associations of PTH and aldosterone levels (5, 7, 8). In addition, results from some small clinical studies indicate that PA may be accompanied by hyperparathyroidism, but these studies were largely limited by inadequate characterization of calcium and vitamin D metabolism (9–11). We therefore evaluated in hypertensive patients derived from the Graz Endocrine Causes of Hypertension (GECOH) study whether PA and its treatment are associated with alterations in PTH levels, parameters of calcium homeostasis, and vitamin D status (12).

Subjects and Methods

Study population

The GECOH study is a diagnostic accuracy study of the aldosterone to active renin ratio (AARR) in screening for PA. The study protocol of the GECOH study has been published previously (12). In brief, the GECOH study population consists of adult patients (age ≥18 yr), who are routinely referred to our outpatient clinic for screening for endocrine hypertension. Main inclusion criterion was arterial hypertension and main exclusion criterion was arterial hypertension and main exclusion criterion was intake of drugs that significantly interfere with the renin angiotensin aldosterone system (RAAS) (i.e. spironolactone, canrenoate, eplerenone, amiloride, triamteren, and/or aliskiren) 4 wk before study entry. Study participants of this single center study at the Medical University of Graz (Graz, Austria) undergo a standardized procedure for PA diagnostics including two determinations of the AARR and a saline infusion test (SIT). Based on these examinations, PA is diagnosed in those patients with at least one AARR of 3.7 ng/dl · μU per milliliter or greater (≥5.7 ng/dl · ng per liter, equivalent to an aldosterone to renin activity ratio of ≥30 ng/dl · ng/ml per hour) and an aldosterone level of 10 ng/dl or greater after the SIT.

Aldosterone computed tomography and adrenal venous sampling was performed in PA patients to differentiate between bilateral idiopathic hyperaldosteronism (IHA) and unilateral aldosterone-producing adrenal adenoma (APA). In a follow-up visit, PA patients were examined at our outpatient clinic after initiation of medical or surgical treatment of PA. Furthermore, all patients were evaluated for parameters of calcium metabolism (serum calcium, vitamin D status, PTH, and urinary calcium) and for other endocrine forms of arterial hypertension (e.g. pheochromocytoma or Cushings disease). In detail, we systematically measured plasma metanephrines and midnight salivary cortisol as screening tests and performed routine confirmatory tests in those patients with significantly elevated levels and clinical symptoms of either Cushings disease or pheochromocytoma. Blood pressure (BP) was measured by the method of Korotkoff after 5 min at rest and by using a sphygmomanometer with an appropriate cuff. Systolic and diastolic BP were measured at both arms and the mean values out of both measurements were recorded. Height and weight were measured wearing light clothes and no shoes. Written informed consent was obtained from all study participants, and the Ethics Committee at the Medical University of Graz approved the study.

Laboratory methods

Laboratory methods have been previously described in detail (12). All blood samplings were performed after an overnight fast between 0800 and 1100 h and after the patients were seated for 10 min. Patients were on an unrestricted Western diet and were advised to avoid both smoking and any medication intake in the morning before blood sampling. Midstream spot urine samples were also collected at baseline. All parameters were measured on a daily or weekly basis at our laboratory. Plasma aldosterone concentration was measured by RIA (active aldosterone RIA DSL-8600; Diagnostic Systems Laboratories, Inc., Webster, TX) with an intra- and interassay coefficient of variation (CV) of 3.3–4.5 and 5.9–9.8%, respectively. Plasma active renin concentrations were also determined by RIA (renin immunoradiometric assay RIA-4541; DRG Instruments GmbH, Marburg, Germany) with an intra- and interassay CV of 0.6–4.5 and 2.7–14.5%, respectively. Intact PTH was determined in plasma by electrochemiluminescence immunoassay on an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany), with a normal range of 15–65 pg/ml and an interassay CV of 5.7–6.3%. Measurement of 25-hydroxyvitamin D [25(OH)D] was performed by means of a chemiluminescence assay (IDS-iSYS 25-hydroxyvitamin D; Immunodiagnostic Systems Ltd., Boldon, UK) on an IDS-iSYS multidiscipline automated analyzer. The within-day CV were 5.5–12.1%, and the interday CV were 8.9–16.9%, respectively. Serum calcium and urinary calcium were measured by using the Roche/Hitachi cobas c system analyzer (Roche Diagnostics). All other parameters were determined by routine laboratory procedures.

Statistical analyses

Depending on their distribution, continuous data are either presented as means ± SD (normally distributed variables) or as medians with interquartile ranges (skewed variables). Variables following a nonnormal distribution were logarithmically transformed before use in parametric analyses. Categorical variables are presented as percentages. Comparisons between patients with essential hypertension (EH) and patients with PA were performed with an unpaired Student’s t test and an analysis of covariance for continuous parameters and with Fisher’s exact test for categorical variables. Paired Student’s t tests were used to evaluate differences in continuous parameters in PA patients before and after treatment, and we calculated Pearson correlation
coefficients to test for associations between continuous variables. A $P < 0.05$ was considered statistically significant, and SPSS version 16.0 (SPSS Inc., Chicago, IL) was used for statistical analyses.

**Results**

Between February 2009 and April 2011, we included 195 patients into the GECOH study. Three patients were subsequently excluded from the present analysis because they refused to undergo the SIT despite elevated AARR, and we could thus not confirm or exclude PA. Among the remaining 192 patients, we diagnosed 10 patients with PA, 182 patients with EH, and no patient with other cause of endocrine hypertension (pheochromocytoma and Cushing’s disease excluded). Furthermore, significant renal artery stenosis was excluded in all PA patients by routine imaging methods. Baseline characteristics for patients with EH and PA at the baseline study visit as well as for PA patients at the follow-up visit are shown in Table 1. As expected, there were marked differences in the parameters of the RAAS between patients with PA and EH. Compared with EH, PTH levels were significantly increased, and serum calcium as well as albumin corrected calcium was significantly decreased in patients with PA (Table 1). There was a nonsignificant trend toward an increased spot urine calcium to creatinine ratio in patients with PA, but there were no significant group differences in 25(OH)D levels. At baseline, only one patient with PA and five patients with EH were on calcium and vitamin D supplementation, and at follow-up, only one patient with PA received additional vitamin D supplementation, whereas no PA patient was treated with any other drugs that could significantly interfere with calcium or bone metabolism. The use of diuretics was not significantly different in patients with PA and EH (50 vs. 39%; $P = 0.516$), and the spot urine calcium to creatinine ratio was similar in patients with and without the use of diuretics [0.20 (0.12–0.32) vs. 0.17 (0.10–0.32), $P = 0.861$].

PTH levels were significantly increased in PA and were reduced to the level of EH after specific treatment (Table 1 and Fig. 1). Considering that body mass index (BMI) is a known predictor of PTH levels, we adjusted for BMI but PTH levels remained significantly elevated in PA compared with EH ($P = 0.019$). Pearson correlation coefficients of aldosterone and PTH in all 10 PA patients were 0.632 ($P = 0.050$) before treatment and $-0.368$ ($P = 0.330$) after treatment. Furthermore, there was no significant correlation between the changes in PTH and in 25(OH)D before and after PA treatment ($r = -0.314; P = 0.256$). Five PA patients were diagnosed as IHA and five patients as APA. In patients with IHA, who were all subsequently treated with MR antagonists (two on 25 mg eplerenone daily and three on 25–50 mg spironolactone).

**TABLE 1.** Clinical and laboratory characteristics of the GECOH study population

<table>
<thead>
<tr>
<th>Variable</th>
<th>Essential hypertension (EH)</th>
<th>PA before treatment (PABT)</th>
<th>PA after treatment (PAAT)</th>
<th>EH vs. PABT P value&lt;sup&gt;a&lt;/sup&gt;</th>
<th>PABT vs. PAAT P value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>182</td>
<td>10</td>
<td>10</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>50.2 ± 15.7</td>
<td>50.1 ± 11.0</td>
<td>51.2 ± 11.5</td>
<td>0.988</td>
<td>0.005</td>
</tr>
<tr>
<td>Females (%)</td>
<td>59.3</td>
<td>60.0</td>
<td>51.0</td>
<td>1.000</td>
<td>0.859</td>
</tr>
<tr>
<td>Females, postmenopausal (%)</td>
<td>53.7</td>
<td>50.0</td>
<td>50.0</td>
<td>0.859</td>
<td>0.859</td>
</tr>
<tr>
<td>Aldosterone (ng/dl)</td>
<td>16.0 (12.3–23.4)</td>
<td>33.6 (24.4–67.8)</td>
<td>31.0 (9.1–53.4)</td>
<td>&lt;0.001</td>
<td>0.267</td>
</tr>
<tr>
<td>PRC (µU/ml)</td>
<td>11.9 (5.9–28.2)</td>
<td>3.1 (2.8–4.4)</td>
<td>16.1 (10.2–24.1)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>AARR (ng/dl · µU per milliliter)</td>
<td>1.5 (0.6–2.8)</td>
<td>11.1 (5.1–21.8)</td>
<td>1.9 (0.7–3.4)</td>
<td>&lt;0.001</td>
<td>0.005</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 ± 6.0</td>
<td>31.0 ± 7.1</td>
<td>NA</td>
<td>0.270</td>
<td>NA</td>
</tr>
<tr>
<td>Systolic blood pressure (mm Hg)</td>
<td>154 ± 23</td>
<td>179 ± 22</td>
<td>149 ± 23</td>
<td>0.006</td>
<td>0.018</td>
</tr>
<tr>
<td>Diastolic blood pressure (mm Hg)</td>
<td>94 ± 13</td>
<td>108 ± 12</td>
<td>96 ± 13</td>
<td>0.005</td>
<td>0.050</td>
</tr>
<tr>
<td>Serum potassium (mmol/liter)</td>
<td>3.9 ± 0.4</td>
<td>3.2 ± 0.3</td>
<td>4.2 ± 0.4</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum sodium (mmol/liter)</td>
<td>141 (140–143)</td>
<td>144 (142–146)</td>
<td>140 (138–142)</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.90 (0.79–1.02)</td>
<td>0.88 (0.74–1.11)</td>
<td>1.16 (0.93–1.44)</td>
<td>0.676</td>
<td>0.005</td>
</tr>
<tr>
<td>PTH (pg/ml)</td>
<td>46.5 ± 20.9</td>
<td>67.8 ± 26.9</td>
<td>43.9 ± 14.9</td>
<td>0.002</td>
<td>0.023</td>
</tr>
<tr>
<td>25(OH)D (ng/ml)</td>
<td>30.5 ± 15.0</td>
<td>33.0 ± 23.7</td>
<td>41.2 ± 22.3</td>
<td>0.748</td>
<td>0.185</td>
</tr>
<tr>
<td>Serum calcium (mmol/liter)</td>
<td>2.35 ± 0.10</td>
<td>2.26 ± 0.10</td>
<td>2.35 ± 0.12</td>
<td>0.013</td>
<td>0.100</td>
</tr>
<tr>
<td>Albumin–corrected calcium</td>
<td>2.23 ± 0.10</td>
<td>2.14 ± 0.10</td>
<td>NA</td>
<td>0.006</td>
<td>NA</td>
</tr>
<tr>
<td>Serum phosphate (mg/dl)</td>
<td>2.92 ± 0.55</td>
<td>2.52 ± 0.68</td>
<td>3.1 ± 0.5</td>
<td>0.029</td>
<td>0.095</td>
</tr>
<tr>
<td>Urinary calcium to creatinine ratio&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.19 (0.11–0.31)</td>
<td>0.33 (0.12–0.53)</td>
<td>NA</td>
<td>0.094</td>
<td>NA</td>
</tr>
</tbody>
</table>

Continuous data are presented as means ± SD or as medians with interquartile ranges. PRC, Plasma renin concentration; NA, not available.

<sup>a</sup> $P$ value for unpaired Student’s $t$ test for continuous variables and for Fisher’s exact test for categorical variables.

<sup>b</sup> $P$ value for paired Student’s $t$ test.

<sup>c</sup> Data for only 167 patients with EH and nine patients with PA.
daily), PTH levels (in picograms per milliliter) were 58.9 ± 15.5 before and 47.1 ± 18.6 after drug treatment (P = 0.132). In patients with APA, who were all treated by removal of a histopathologically confirmed adrenal adenoma, PTH levels were 76.7 ± 34.4 before and 40.6 ± 11.1 after surgery (P = 0.077). Follow-up visits were performed after a median of 3.7 months (range 0.3–19.5 months) after the start of PA treatment. In detail, follow-up visits were performed after a median of 1.0 month (range 0.4–15.9 months) after adrenal surgery in patients with APA and after a median of 6.3 months (range 0.3–19.5 months) after the start of MR blocker therapy in patients with IHA. BP in treated PA patients was either improved or was similar compared with baseline values but with a reduced number or dose of antihypertensive drugs. In addition, we performed a second follow-up examination among eight PA patients after a median of 22.2 months (range 3.4–27.6 months) after the start of PA treatment. In that follow-up visit, PTH levels (in picograms per milliliter) remained significantly reduced compared with baseline (41.4 ± 11.4 vs. 59.4 ± 21.1, P = 0.037).

Discussion

We have shown that compared with EH, patients with PA have higher PTH levels that are significantly reduced after targeted treatment of PA. These differences in PTH levels were accompanied by reduced baseline serum calcium levels in PA patients, and we observed a nonsignificant trend for increased baseline urinary calcium excretion in PA.

Previous studies in rats demonstrated increased urinary and fecal calcium excretion and bone loss in the setting of experimental aldosteronism that could be attenuated by spironolactone treatment (3–5, 13, 14). Our results support the concept that PA may lead to secondary hyperparathyroidism. We confirm the finding of a previous study that showed similar data in PA patients but did not report on vitamin D status (10). In general, the results of the GECOH study support the concept that aldosterone excess in the setting of PA may decrease serum calcium levels, likewise by increased urinary calcium loss, and may thereby contribute to secondary hyperparathyroidism. Importantly, PA treatment in the GECOH study had a remarkable suppressive effect on PTH levels. In fact, after targeted treatment of PA, PTH levels in patients on MR antagonists or after adrenal surgery were similar compared with patients with EH. Changes in PTH levels appeared to be more pronounced in patients with APA treated by surgery compared with patients with IHA treated by MR antagonists, but we should be cautious with interpreting results of very small subgroups. Whether PTH elevations may partially underlie the excess cardiovascular risk in PA warrants further studies.

Apart from PA, the proposed link of aldosterone and PTH may be also of clinical relevance when considering the widespread use of spironolactone for the treatment of heart failure patients, who are also prone to secondary hyperparathyroidism (15). Interestingly, it has been observed that the use of spironolactone is associated with reduced fracture risk in heart failure patients, a result that may hypothetically be driven by bone effects of PTH (16). Hence, an important research question for future studies is the impact of MR antagonists on PTH and calcium metabolism in patients without PA. Apart from this, it is interesting to note that there are reports on hypercalcemia and suppressed PTH in adrenal insufficiency that can be corrected after hormonal substitutive therapy (17). Although our study aimed to test whether PA is associated with hyperparathyroidism, we have to acknowledge that there is also evidence for a potential reverse causation, i.e., that PTH itself may stimulate the RAAS (8, 18–21). Future studies should therefore evaluate the complex interplay of PTH and RAAS and should clarify whether PTH measurements might be useful for diagnostics of PA.

Our results are limited by the relatively small sample size of patients with PA, the observational nature of our study, and some limitations related to the characterization of calcium metabolism (e.g. missing data on 24 h urinary calcium excretion, follow-up urinary samples, or ionized serum calcium). Furthermore, our work is only a secondary outcomes analysis of the GECOH study and our data were derived from a Caucasian cohort of hypertensive patients. Our findings may therefore not be generalizable to other study populations.

In conclusion, our results show that PA patients are prone to secondary hyperparathyroidism that can be suc-
cessfully treated with MR antagonists or adrenal surgery. Further studies are warranted to evaluate whether PTH has implications for diagnostic procedures for PA and whether MR antagonists have, beyond PA, a general impact on PTH and calcium metabolism.

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Disclosure Summary: The authors have nothing to disclose.

References