Homoarginine in Patients With Primary Hyperparathyroidism

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Abstract: Background: Low levels of the amino acid homoarginine and parathyroid hormone (PTH) excess are both independently related to an increased risk of cardiovascular morbidity and mortality. Accumulating evidence points to a mutual interplay between homoarginine and PTH. The authors therefore aimed to investigate circulating homoarginine levels in patients with and without primary hyperparathyroidism (PHPT). Methods: The authors performed a cross-sectional analysis of serum homoarginine levels in 59 patients with mild and severe PHPT and in 92 control persons matched for age, sex and estimated glomerular filtration rate. Results: Median PTH and serum homoarginine concentrations were 99.1 (79.7–120.2) pg/mL and 1.16 (0.95–1.66) µmol/L in patients with PHPT (79.7% female; 42.4% with normocalcemia) as compared with 45.8 (36.4–53.9) pg/mL and 1.62 (1.33–2.04) µmol/L in the control group (P < 0.001 for both), respectively. The authors observed no statistically different differences between cases and controls for 25-hydroxyvitamin D [25(OH)D], serum albumin, hemoglobin, waist-to-hip ratio, C-reactive protein and NT-pBP values. Multivariate analysis of covariance revealed that patients with PHPT had significantly lower homoarginine levels than controls (P < 0.001). This difference remained significant after adjusting for multiple confounders such as 25(OH)D, body mass index, LDL cholesterol, albumin, calcium, hemoglobin, smoking status and current antihypertensive medication. The difference of homoarginine levels persisted even after exclusion of patients with estimated glomerular filtration rate < 60 ml/min (P = 0.003) and 25(OH)D levels < 30 ng/mL (P = 0.001), respectively. Conclusions: Patients with PHPT have lower homoarginine levels compared with matched controls irrespective of age, sex, kidney function and 25(OH)D status. Further studies are needed to evaluate whether low homoarginine accounts for higher cardiovascular risk conferred by PTH excess.


Parathyroid hormone (PTH) is synthesized by parathyroid glands in response to low circulating calcium and plays a pivotal role in regulating calcium-phosphate homeostasis. Increased PTH levels have been linked to hypertension, endothelial dysfunction, vascular stiffness and myocardial dysfunction.1–5 Prospective studies in community-based samples and patients at coronary risk have identified elevated PTH as a strong and independent predictor of cardiovascular (CVD) mortality.6–9 A recent meta-analysis of prospective investigations supports the notion that PTH is related to fatal CVD events even in patients without chronic kidney disease.8 Along with this, patients with mild, moderately severe and severe primary hyperparathyroidism (PHPT) are at higher risk of CVD death.9,10 Considering the CVD burden resulting from PTH excess, it is important to elucidate the mechanisms of nonclassical deleterious effects of PTH on the CVD system. Growing evidence points to low homoarginine, which is a cationic amino acid derivative detected in seeds of grass peas (Lathyrus sativus and Lathyrus cicera) 50 years ago, as novel mediator of CVD risk in patients with elevated PTH levels.11–15 Low homoarginine levels have emerged as powerful predictor of all-cause and CVD mortality in both 3,305 patients referred to coronary angiography and 1,244 patients with diabetes on maintenance hemodialysis.17 Cross-sectional studies in elderly women and patients referred to coronary angiography identified lower homoarginine levels in patients with higher PTH levels.18–19 Thus, the authors set out with the hypothesis that decreased homoarginine levels may account for some of the CVD damage, which is seen in patients with high PTH levels.

To date, studies evaluating the homoarginine status in patients with PHPT are missing. The authors therefore aimed to compare circulating homoarginine levels between patients with mild to severe PHPT and controls persons thoroughly matched for age, sex and estimated glomerular filtration rate (eGFR) without PHPT.

Subjects and Methods

Participants

Cases

In a cross-sectional study, the authors compared 59 consecutive PHPT patients with 92 controls matched for age, sex and eGFR.
For the present analysis PHPT was defined according to proceedings of the third international workshop on diagnosing asymptomatic PHPT.20

Patients with PHPT were identified in the outpatient clinic of the Division of Endocrinology and Metabolism (Department of Internal Medicine) and the Department of Cardiology of the Medical University of Graz and through regional file extraction of diagnosis.

Patients with PHPT have been enrolled in the Effects of eplerenone on parathyroid hormone levels in patients with primary hyperparathyroidism (EPATH) trial (ISRCTN33941607), which is an ongoing, randomized, double-blind, placebo-controlled trial to evaluate the effects of the mineralocorticoid receptor antagonist eplerenone in patients with PHPT. Detailed descriptions of the baseline examination in EPATH have been published previously.21 In brief, inclusion criteria are as follows: men and women aged at least 18 years with PHPT, who (1) do not meet criteria for surgical treatment or (2) in whom surgery is recommended, but not randomized because of patient and/or physician preference or (3) perceived medical contraindications. Exclusion criteria at baseline were (1) 25-hydroxyvitamin D [25(OH)D] concentration <20 ng/dL (50 nmol/L), (2) eGFR ≤50 mL/min, (3) serum potassium >5.0 mEq/L (mmol/L), (4) pregnancy or lactation, (5) drug intake as part of another clinical study 4 weeks before enrollment into the EPATH trial and/or during the active study period, (6) any disease with an estimated life expectancy below 1 year, (7) severe acute or chronic liver diseases (Child-Pugh Class C) and (8) concurrent intake of potassium sparing drugs, for example, diuretics (amiloride and triamterene) or CPY3A4-inhibitors and ongoing potassium supplementation.

Controls

The authors recruited controls from The Styrian Hypertension Study, which is an ongoing prospective cohort study with the main objective to study biomarkers in relation to arterial hypertension and CVD risk. Study participants (age ≥18 years) were prospectively recruited from the Division of Endocrinology and Metabolism at the Medical University of Graz, Austria. Main exclusion criteria were stroke or myocardial infarction in the previous 4 weeks, pregnancy or pregnancy lactation and estimated life expectancy of less than 1 year.

Written informed consent was obtained from all study participants. The EPATH Trial and The Styrian Hypertension Study were approved by the ethics committee at the Medical University Graz, Austria. The studies are in accordance with the Declaration of Helsinki.

Baseline Measurement

Blood sampling procedures were identical between cases and controls and have been previously described.21 In brief, blood sampling was performed in the morning (7–11 AM) after an overnight fast and after 10 minutes in the sitting position. All blood samples were centrifuged within 1 hour after sampling and were analyzed at latest 4 hours after blood collection. Before analysis or freezing, all samples were kept at room temperature, with the exception of the samples for the determination of iPTH (1–84), which were kept at 4°C. Aliquots were stored long term at −70 to 80°C at the Biobank Institute of the Medical University of Graz.

Measurement of iPTH (1–84) (pg/mL) was performed by electrochemiluminiscence immunoassay “ECLIA” (Elecys immunoassay analyzer; CobasW; Roche Diagnostics GmbH, Mannheim, Germany; reference range, 15–65 pg/mL, interassay coefficient of variation 3.0%–6.5% for PTH 26.7–261 pg/mL). Homoarginine was measured using reverse phase high-performance liquid chromatography method. Intraday coefficients of variation (CVs) at different concentrations (mean levels) were 4.7% (1.21 μmol/L) and 2.2% (3.53 μmol/L), and between-day CVs were 7.9% (1.25 μmol/L) and 6.8% (3.66 μmol/L), respectively.
eGFR was calculated according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula as published.22 Measurement of 25(OH)D was performed by means of a chemiluminescence assay (IDS-isYS 25-hydroxyvitamin D; Immunodiagnostics Systems Ltd., Boldon, United Kingdom) on an IDS-isYS multidiscipline automated analyzer. The within-day CV were 5.5% to 12.1%, and the interday CV were 8.9% to 16.9%, respectively.

NT-pro(p)-BNP was measured using an electrochemiluminescence immunoassay based on a polyclonal antibody-based sandwich chemiluminescence assay (Roche Diagnostics) using an autoanalyzer (Elecys 2010). All other parameters were determined by routine laboratory procedures.

Brachial artery pressure was measured with an automated oscillometric device after the patient had rested in the sitting position for 10 minutes. At least 2 consecutive systolic BP and diastolic BP measurements were taken with a minimum interval of 60 seconds.

Statistics

Continuous variables are expressed as mean ± SDs or (those with skewed distribution) as medians and interquartile ranges and categorical variables as percentages. For unadjusted comparison of data at baseline between patients with PHPT and controls, the unpaired t-test was used for data with normal distribution and the Mann-Whitney’s U test for data with non-normal distributions. Categorical variables were compared by using the χ² trend test.

Pearson’s correlation test was performed to evaluate potential correlations between PTH and homoarginine overall and in cases and controls, respectively.

The distribution of serum homoarginine levels between patients with PHPT and matched controls was analyzed by analysis of covariance (ANCOVA) after adjustment for age, sex, body mass index (BMI), LDL cholesterol, eGFR, 25(OH)D, serum (S) calcium, hemoglobin, serum albumin, NT-pBNP, C-reactive protein (CRP) and smoking status. Because previous studies reported a significant variation of homoarginine levels according to intake of antihypertensive drugs, the authors additionally adjusted for the use of ACE inhibitors, β-blockers and diuretics.23,24 ANCOVA has been repeated in subgroups stratified according to kidney function, 25(OH)D and smoking status.

Data were analyzed using SPSS 17.0 statistical package (SPSS, Inc., Chicago, IL). A P value of <0.05 was considered statistically significant.

RESULTS

The clinical and biochemical characteristics data of the 59 PHPT (79.7% female) and the 92 matched controls (66.3% female) are given in Table 1. The PHPT group included 34 (57.6%) patients with hypercalcemia. Within the PHPT and control group, 92.5% and 100%, respectively, of the female participants were postmenopausal. No women with ongoing HRT were observed within the control and cases group, respectively.

Median (and mean) PTH and serum homoarginine levels were 99.1 (79.7–120.2) pg/mL (mean: 116.7 ± 66.6 pg/mL) and 1.16 (0.95–1.66) μmol/L (mean: 1.29 ± 0.51 μmol/L) in...
TABLE 1. Clinical and biochemical characteristics data of 59 PHPT and 92 control subjects

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PHPT (n = 59)</th>
<th>Matched controls (n = 92)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>66.9 ± 10.2</td>
<td>66.5 ± 5.8</td>
<td>0.784</td>
</tr>
<tr>
<td>Sex: females, %</td>
<td>79.7</td>
<td>66.3</td>
<td>0.097</td>
</tr>
<tr>
<td>Waist-to-hip ratio</td>
<td>0.92 ± 0.08</td>
<td>0.94 ± 0.07</td>
<td>0.140</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27.4 ± 4.6</td>
<td>29.6 ± 3.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Parathyroid hormone, pg/mL</td>
<td>99.1 (79.7–120.2)</td>
<td>45.8 (36.4–53.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum homoarginine, µmol/L</td>
<td>1.16 (0.95–1.66)</td>
<td>1.62 (1.33–2.04)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (mL·min⁻¹·1.73 m⁻²)</td>
<td>79.2 ± 13.2</td>
<td>75.3 ± 13.9</td>
<td>0.121</td>
</tr>
<tr>
<td>Serum albumin, g/dL</td>
<td>4.56 ± 0.28</td>
<td>4.49 ± 0.30</td>
<td>0.145</td>
</tr>
<tr>
<td>Hemoglobin, g/L</td>
<td>13.9 ± 1.3</td>
<td>14.1 ± 1.1</td>
<td>0.346</td>
</tr>
<tr>
<td>Serum total calcium, mmol/L</td>
<td>2.63 ± 0.13</td>
<td>2.43 ± 0.09</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum phosphate, mmol/L</td>
<td>0.80 ± 0.12</td>
<td>1.01 ± 0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25-hydroxyvitamin D, ng/mL</td>
<td>33.0 (27.5–44.3)</td>
<td>32.5 (25.6–37.7)</td>
<td>0.089</td>
</tr>
<tr>
<td>C-reactive protein, mg/L</td>
<td>1.0 (0.6–3.0)</td>
<td>2.15 (1.00–3.60)</td>
<td>0.638</td>
</tr>
<tr>
<td>NT-pBNP, pg/mL</td>
<td>113.0 (60.0–189.0)</td>
<td>120.0 (65.0–166.5)</td>
<td>0.792</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>10.2</td>
<td>7.6</td>
<td>0.585</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dL</td>
<td>101.6 ± 32.6</td>
<td>117.8 ± 32.3</td>
<td>0.021</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>67.1 ± 17.9</td>
<td>62.8 ± 16.8</td>
<td>0.228</td>
</tr>
<tr>
<td>Triglycerides, mg/dL</td>
<td>107.2 ± 55.7</td>
<td>123.5 ± 66.6</td>
<td>0.120</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>144 ± 21</td>
<td>141 ± 17</td>
<td>0.377</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>88 ± 11</td>
<td>84 ± 11</td>
<td>0.027</td>
</tr>
<tr>
<td>ACE inhibitors, %</td>
<td>22.0</td>
<td>41.3</td>
<td>0.021</td>
</tr>
<tr>
<td>β-Blockers, %</td>
<td>40.7</td>
<td>58.7</td>
<td>0.045</td>
</tr>
<tr>
<td>Diuretics, %</td>
<td>28.8</td>
<td>52.2</td>
<td>0.007</td>
</tr>
</tbody>
</table>

Values are given as median (25th, 75th percentile), as mean with SD and as percentage for categorical data.

For unadjusted comparison between cases and controls, the unpaired t test was used for data with normal distribution and the Mann-Whitney U test for data with considerable variance. Categorical variables were compared by using the χ² trend test.

a eGFR, estimated glomerular filtration rate according to the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula; PHPT, primary hyperparathyroidism.

patients with PHPT as compared with 45.8 (36.4–53.9) pg/mL (mean: 45.6 ± 10.8 pg/mL) and 1.62 (1.33–2.04) µmol/L (mean: 1.74 ± 0.60 µmol/L) in the control group (P < 0.001 for both, respectively).

Mean age was 66.9 ± 10.2 years in patients with PHPT as compared with 66.5 ± 5.8 years in the control group (P = 0.784). There were statistically significant differences in the mean values between groups for serum homoarginine, PTH, calcium, phosphate, BMI, LDL cholesterol and ongoing antihypertensive treatment. In contrast, no statistically differences were observed between cases and controls for 25-hydroxyvitamin D [25(OH)D], albumin, calcium, hemoglobin, smoking status and ongoing antihypertensive medication.

In view of the strong dependence of PTH and homoarginine on kidney function, the authors repeated the multivariate ANCOVA in patients with eGFR values ≥60 mL/min (PHPT group: n = 53 [89.7%]; control group: n = 77 [83.7%]) and found persistently varying homoarginine levels between cases and controls (P = 0.003) (Figure 1). Moreover, the difference between homoarginine levels did not materially change after repeating the analysis in patients with 25(OH)D ≥30 ng/mL (PHPT group: n = 38 [64.4%]; control group: n = 54 [58.7%]) (P = 0.001). Finally, the authors repeated the multivariate analysis in nonsmokers (PHPT: n = 53 [89.8%]; controls: n = 85 [92.4%]) and found that the difference between homoarginine levels in cases and controls persisted (P < 0.001).

DISCUSSION

In this study, the authors investigated circulating homoarginine levels in patients with PHPT and a matched control group. Even after considering multiple confounders, the authors observed significantly lower serum homoarginine levels in patients with PHPT than in controls. The difference between homoarginine levels between these 2 groups persisted in nonsmokers, after exclusion of patients with eGFRs below 60 mL/min and after exclusion of those with 25(OH)D below 30 ng/mL, respectively.

The present findings indicate direct and/or indirect interactions between homoarginine and PTH resulting in lower homoarginine levels in patients with PHPT. This may be of clinical relevance on the background of the observed elevated CVD risk related to PTH excess and low homoarginine. This is
in line with a considerable attenuation of homoarginine-related risk of mortality after additional consideration of PTH in female nursing home residents. This notion is further supported by preliminary data from the SOS-HIP study including female nursing home patients in which lower homoarginine is related to a greater risk for all-cause mortality exclusively in subjects with high PTH levels.

Ring et al recently postulated that the CVD risk of patients with PHPT might be in part related to “indirect” effects rather than to direct effects of PTH on the CVD system. Endothelial dysfunction is strongly linked to nitric oxide synthase activity. Previous studies in patients with PHPT documented lower endothelial-mediated vasodilatation compared with age-matched controls. Given that homoarginine in parallel to arginine acts as a substrate and cofactor of the nitric oxide synthase, the authors speculate that low homoarginine—in terms of “homoarginine paradox”—aggravates endothelial dysfunction in the setting of PTH excess. Mechanistic and observational studies in subjects with PHPT are therefore needed to evaluate whether effects on the vasculature, which have been previously attributed to elevated PTH, are actually due to low homoarginine downstream of the PTH excess.

In humans, homoarginine is formed and regulated by 3 basic ways: (1) in an alternative urea cycle, homoarginine is generated from lysine catalyzed by the ornithine transcarbamoylase, (2) by a transamidation reaction catalyzed by the mitochondrial arginine:glycine amidinotransferase (AGAT), which is predominantly expressed in the kidney and according to previous findings might strongly depend on kidney function and (3) varying circulating levels of homoarginine might result from altered arginase activity, which degrade homoarginine to lysine and urea, and contribute to the development of endothelial dysfunction.

<table>
<thead>
<tr>
<th>Model Adjustment</th>
<th>PHPT Mean homoarginine (95% CI)</th>
<th>Controls Mean homoarginine (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted</td>
<td>1.20 (1.09–1.31)</td>
<td>1.65 (1.53–1.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 1 adjusted for age</td>
<td>1.20 (1.09–1.31)</td>
<td>1.65 (1.54–1.77)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2 + sex</td>
<td>1.21 (1.11–1.32)</td>
<td>1.63 (1.52–1.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3 + BMI and LDL cholesterol</td>
<td>1.22 (1.10–1.34)</td>
<td>1.64 (1.53–1.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 4 + eGFR&lt;sub&gt;CKD–EPI&lt;/sub&gt;</td>
<td>1.22 (1.10–1.35)</td>
<td>1.63 (1.52–1.75)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 5 + 25-hydroxyvitamin D</td>
<td>1.23 (1.11–1.36)</td>
<td>1.63 (1.52–1.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 6 + serum calcium</td>
<td>1.18 (1.05–1.33)</td>
<td>1.66 (1.53–1.79)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 7 + hemoglobin, serum albumin</td>
<td>1.19 (1.05–1.34)</td>
<td>1.66 (1.53–1.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 8 + NT-pBNP, CRP</td>
<td>1.20 (1.06–1.36)</td>
<td>1.65 (1.52–1.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 9 + smoking status</td>
<td>1.21 (1.07–1.36)</td>
<td>1.64 (1.52–1.78)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 10 + ACE-I, β-Blocker, diuretics</td>
<td>1.19 (1.05–1.36)</td>
<td>1.66 (1.51–1.82)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

ACE-I, ACE inhibitors; BMI, body mass index; CRP, C-reactive protein; NT-pBNP, N-terminal pro B-type natriuretic peptide; PHPT, primary hyperparathyroidism.
In the present GFR-matched case-control investigation, the difference between homoarginine levels persisted even after exclusion of patients with impaired kidney function. The authors therefore suggest that lower kidney function and subsequently decreased homoarginine formation, for example, due to lower AGAT activity, might not be a relevant mechanism for entailing low homoarginine levels found in patients with PHPT. The comparable low homoarginine levels in patients with PHPT and renal patients (with secondary hyperparathyroidism) on hemodialysis however tempt to speculate that high PTH concentrations might result in lower homoarginine levels in both settings. Whether PTH directly interacts with above-stated enzymes related to homoarginine metabolism however remains a matter of research. The higher age of participants in the present case group might additionally contribute to lower homoarginine levels, which are similarly low as reported in elderly female nursing home patients.

One further potential mechanism leading to varying homoarginine levels is based on an interplay between PTH and the growth hormone/IGF-1 axis. AGAT gene expression and subsequent homoarginine formation is regulated by growth hormone. Given that PTH induces IGF-1 expression, for example, in bone tissue, the authors speculate that varying homoarginine levels between patients with and without PTH excess might also result from modulating (indirect) effects of PTH on IGF-1 leading to an altered AGAT activity.

Further mechanistic studies demonstrated that PTH stimulates the ornithine decarboxylase (ODC) activity, for example, in human osteosarcoma cells and osteoblasts and by stimulating cAMP and intracellular Ca2+. A connection between increased ornithine metabolism and lower homoarginine concentration cannot be argued conclusively. A repercussion of low ornithine concentration to the AGAT enzyme and homoarginine metabolism however cannot be excluded because of the multi-substrate ping pong mechanism, which involves reactions of metabolites depending on their concentration ratios. Interestingly, polymorphisms of the ornithine decarboxylase antizyme, an inhibitor of the ODC, are related to a progression of common carotid intima-media thickness and risk of CVD development.

Due to structural similarities between the ornithine and lysine decarboxylase (LDC), it would be conceivable that PTH modulates homoarginine metabolism by impacting on LDC activity, too. It is further unclear whether dyshomeostasis of calcium and phosphate in the setting of PTH excess contributes to a decline of homoarginine levels. Alternatively, the present relationship between homoarginine and PTH might also be explained by altered availability of arginine for homoarginine formation.

Further modes of interactions between homoarginine and PTH have been otherwise indicated in experimental studies. PTH acts through binding to the PTH/PTH-related protein receptor (PTH/PTHrP receptor = PTH1R), which is highly expressed in the bone and kidney. The amino-terminus of the ligand participates in the stimulation of the PTH1R coupled cAMP pathway. In LLC-PK1-derived and osteoblast-like cells transfected with the human PTH1R, the substitution of homoarginine to synthetic PTH-related peptides resulted in a 30-fold higher potency compared with the native PTH-related peptide with respect to activation of the PTH1R and the ensuing cAMP pathway. However, whether the PTH-receptor interaction is modified by homoarginine in humans and in a clinically relevant manner remains to be explored in further studies.

The additional consideration of parameters reflecting wasting, such as serum albumin and hemoglobin, did not materially change these results. Likewise, the authors’ analysis indicated that homoarginine levels are lower in the setting of PTH excess independent of the 25(OH)D status, which is a major regulator of PTH secretion. Previous investigations additionally noted significant variations of homoarginine levels according to smoking status. In this study, the difference of homoarginine levels between cases and controls persisted after both adjustment for smoking status and when nonsmokers were analyzed separately.

**Limitations and Strengths**

The observational design of this study precludes conclusions regarding causal relationships. The authors cannot rule out that differences between unidentified anthropometric or biochemical parameters such as lysine, arginine, ornithine and arginine-to-ornithine ratio (reflecting arginase activity) may have influenced the observed differences of homoarginine levels. In a next step, the determination of varying activities of enzymes involved in homoarginine metabolism such as ornithine transcarbamoylase, AGAT and arginases should further elucidate the link between low homoarginine and PTH excess. A further limitation of this study was the relatively small sample size, which excluded the possibility to further stratify the analysis according to patients with mild and severe PHPT. Whether, the missing correlation between PTH and homoarginine levels in patients with PHPT indicates a threshold effect of PTH on homoarginine formation remains to be determined.

There are several strengths in this investigation. Patients and controls were carefully matched according to age, sex and kidney function and were recruited within the same ambulatory setting and research team. Furthermore, 25(OH)D, NT-proBNP, CRP, waist-to-hip ratio and hemoglobin did not significantly vary between cases and controls. The primary nature of PTH excess within these patients limits the possibility of reverse causality; thus, the authors suggest that the attenuation of PTH due to low homoarginine levels is rather unlikely.

**CONCLUSIONS**

Irrespective of the underlying mechanisms, it seems conceivable that homoarginine levels are lower in patients with PTH excess. Considering the strong impact of low homoarginine and high PTH levels on CVD morbidity and mortality risk, these data are of clinical relevance. Hence, further observational and mechanistic studies are needed to evaluate the mechanisms underlying the inverse relationship between PTH and homoarginine and the ensuing impact on CVD health.

**REFERENCES**

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