Diuretics, calciuria and secondary hyperparathyroidism in the Chronic Renal Insufficiency Cohort (CRIC)

Tamara Isakova¹, Cheryl A. M. Anderson², Mary B. Leonard³,⁴, Dawei Xie⁴, Orlando M. Gutiérrez⁵, Leigh K. Rosen⁶, Jacquie Theurer⁷, Keith Bellovich⁸, Susan P. Steigerwalt⁶, Ignatius Tang⁷, Amanda Hyre Anderson⁴, Raymond R. Townsend⁹, Jiang He², Harold I. Feldman⁴,⁸, and Myles Wolf⁴ On Behalf of the Chronic Renal Insufficiency Cohort (CRIC) Study Group

¹Division of Nephrology and Hypertension, Department of Medicine, University of Miami Miller School of Medicine, Miami, FL, USA, ²Welch Center for Prevention, Epidemiology and Clinical Research and the Department of Epidemiology, Johns Hopkins University, Baltimore, MA, USA, ³Department of Pediatrics, the Children’s Hospital of Philadelphia, University of Pennsylvania School of Medicine, Philadelphia, PA, USA, ⁴Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania School of Medicine, Philadelphia, PA, USA, ⁵Division of Nephrology, Department of Medicine, MetroHealth Medical Center, Cleveland, OH, USA, ⁶Division of Nephrology, Department of Medicine, St. John’s Health System, Detroit, MI, USA, ⁷Section of Transplant Medicine and Nephrology, Department of Medicine, University of Illinois Medical Center, Chicago, IL, USA, ⁸Departments of Medicine, University of Pennsylvania, Philadelphia, PA, USA and ⁹Departments of Medicine and Epidemiology, Tulane University, New Orleans, LU, USA

Correspondence and offprint requests to: Myles Wolf; E-mail: mwolf2@med.miami.edu

Abstract

Background. Secondary hyperparathyroidism is a common complication of chronic kidney disease (CKD) that is associated with bone disease, cardiovascular disease and death. Pathophysiological factors that maintain secondary hyperparathyroidism in advanced CKD are well-known, but early mechanisms of the disease that can be targeted for its primary prevention are poorly understood. Diuretics are widely used to control volume status and blood pressure in CKD patients but are also known to have important effects on renal calcium handling, which we hypothesized could alter the risk of secondary hyperparathyroidism.

Methods. We examined the relationship of diuretic treatment with urinary calcium excretion, parathyroid hormone (PTH) levels and prevalence of secondary hyperparathyroidism (PTH ≥ 65 pg/mL) in a cross-sectional study of 3616 CKD patients in the Chronic Renal Insufficiency Cohort.

Results. Compared with no diuretics, treatment with loop diuretics was independently associated with higher adjusted urinary calcium (55.0 versus 39.6 mg/day; P < 0.001), higher adjusted PTH [67.9, 95% confidence interval (CI) 65.2–70.7 pg/mL, versus 52.8, 95% CI 51.1–54.6 pg/mL, P < 0.001] and greater odds of secondary hyperparathyroidism (odds ratio 2.1; 95% CI 1.3–2.6). Thiazide monotherapy was associated with lower calcium (25.5 versus 39.6 mg/day; P < 0.001) but only modestly lower PTH levels (50.0, 95% CI 47.8–52.3, versus 520.8, 95% CI 51.1–54.6 pg/mL, P = 0.04) compared with no diuretics. However, coadministration of thiazide and loop diuretics was associated with blunted urinary calcium (30.3 versus 55.0 mg/day; P < 0.001) and odds of hyperparathyroidism (odds ratio 1.3 versus 2.1; P for interaction = 0.05) compared with loop diuretics alone.

Conclusions. Loop diuretic use was associated with greater calciuria, PTH levels and odds of secondary hyperparathyroidism compared to no treatment. These associations were attenuated in patients who were coadministered thiazides. Diuretic choice is a potentially modifiable determinant of secondary hyperparathyroidism in CKD.

Keywords: calciuria; chronic kidney disease; diuretics; parathyroid hormone

Introduction

Chronic kidney disease (CKD) is a growing public health problem estimated to affect up to 13% of US adults or ~26 million Americans [1]. Among the most common complications of CKD is disordered mineral metabolism due to altered calcium and phosphate balance, deficiencies in the vitamin D axis and secondary increases in circulating concentrations of fibroblast growth factor 23 (FGF23) and parathyroid hormone (PTH) [2–5]. These pathophysiological alterations are independent risk factors for bone loss, fracture, cardiovascular disease and death in CKD patients and the general population [6–11].

For decades, the primary therapeutic focus of managing disordered mineral metabolism in CKD has been the control...
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of secondary hyperparathyroidism in dialysis patients using PTH-suppressive therapies. Administering these complex regimens in the dialysis setting is labor and time intensive, costly and frequently complicated by side effects. The recognition that secondary hyperparathyroidism begins long before patients reach dialysis stimulated clinical practice guidelines to advocate regular PTH screening beginning in earlier stages of CKD and initiation of therapy once PTH levels exceed stage-specific thresholds [12]. However, despite the recommendation for earlier treatment, the cornerstone of clinical management remains secondary prevention of complications of established secondary hyperparathyroidism rather than primary prevention of secondary hyperparathyroidism itself.

Designing primary prevention strategies requires knowledge of the pathophysiological triggers of secondary hyperparathyroidism in early CKD. However, while much is known about normal parathyroid metabolism and the mechanisms that maintain secondary hyperparathyroidism in advanced renal failure, its early pathophysiological triggers remain mostly elusive. Previous large studies in the general population reported that excessive calciuria driven by loop diuretics is associated with elevated PTH, bone loss and fractures [13–16]. Other studies from the general population, including a randomized trial, demonstrated that treatment with thiazide diuretics, which reduce calciuria, improved bone mineralization and reduced fractures [17–19]. Although diuretics are widely used to control volume status and blood pressure in CKD patients, there are sparse data on the impact of these drugs on secondary hyperparathyroidism in CKD. Using a large well-characterized cohort of CKD patients, we tested the hypotheses that patients treated with loop diuretics would have greater levels of calciuria and PTH and a higher prevalence of secondary hyperparathyroidism than patients who were not treated with diuretics and that patients treated with thiazide diuretics would have lower levels of calciuria and PTH and a lower prevalence of secondary hyperparathyroidism.

Materials and methods

Description of cohort

The Chronic Renal Insufficiency Cohort (CRIC) is a multicenter prospective cohort study of risk factors for cardiovascular disease and progression of CKD [20]. Patients aged 21–74 years with an age-stratified estimated glomerular filtration rate (eGFR) of 20–70 mL/min/1.73m² were enrolled. Since CKD is more common among ethnic minorities, blacks were over-sampled, and the ancillary Hispanic CRIC (HCRIC) study enrolled 327 additional Hispanic participants. Exclusion criteria included inability to provide consent, institutionalization, enrollment in other research studies, pregnancy, New York Heart Association class III–IV heart failure, HIV, cirrhosis, myeloma, renal cancer, recent chemotherapy or immunosuppressive therapy, polycystic kidney disease, organ transplantation or prior treatment with dialysis for >1 month. The CRIC protocol was approved by the institutional review boards at each of the seven primary sites (University of Pennsylvania, Johns Hopkins University, Case Western Reserve University, University of Michigan, University of Illinois at Chicago, Tulane University Health Science Center and Kaiser Permanente of Northern California). All participants provided written informed consent.

Data collected at baseline included demographics, medical history, medications used in the past 30 days, blood pressure, anthropometry, fasting blood samples, 24-h urine specimens and the National Cancer Institute’s Diet History Questionnaire (DHQ). The DHQ is a food frequency questionnaire that estimates usual dietary intake by surveying portion size and frequency of consumption of 124 food items during the past year [21]. Dietary data were manually reviewed for completeness and analyzed for daily nutrient intake using NCI’s DietCalc software. Comprehensive metabolic panels and urinary sodium, potassium, calcium and creatinine were measured using standard assays. Plasma PTH was measured using an intact assay [Scantibodies, Santee, CA; coefficient of variation (CV) of <5%]. Serum 25-hydroxyvitamin D (25D), quantified by radioimmunoassay (DiaSorin, Stillwater, MN; CV < 3%), was available in a subset of 327 participants. Serum 1,25-dihydroxyvitamin D (1,25D), quantified by competitive chemiluminescent immunoassay (Heartland Assays, Ames, IA; CV < 12%), was available in 326 participants.

Study population

We evaluated 3616 of the 3939 total CRIC and HCRIC participants who had complete baseline data on diuretic treatment status and PTH levels. Dietary data were available for 2741 participants. The remainder either did not complete the DHQ, or their data were excluded by the CRIC data coordinating center because of implausible values for total energy intake (i.e. ≤600 or ≥4000 kcal for women and ≤800 or ≥5000 kcal for men). Twenty-four-hour urinary data were available for 3449 participants. The proportion of participants with missing dietary and 24-h urine data was similar across the diuretic treatment groups.

Exposures and outcomes

The primary outcomes were urinary calcium excretion, PTH levels and presence of secondary hyperparathyroidism, defined as PTH ≥265 pg/mL [5]. The primary exposure was diuretic treatment, categorized as monotherapy with loop diuretics (n = 1083); monotherapy with thiazide diuretics (n = 723); combined therapy with loop and thiazide diuretics (n = 289) and no diuretic use (n = 1521). Participants reporting treatment with bumetanide, ethacrynic acid, furosemide or torsemide were considered as treated with loop diuretics. Participants reporting treatment with chlorothalidone, chlorthalidone, hydrochlorothiazide, indapamide or metolazone or any combination therapy that included these agents were considered as treated with thiazide diuretics.

Statistical analysis

We compared demographic, clinical, laboratory, dietary and crude urinary data across the diuretic treatment groups using ANOVA, Kruskal Wallis, or χ² tests as appropriate. Many clinical characteristics guide practitioners’ decision to treat patients with diuretics and which diuretic class they choose. To guide subsequent analyses, we identified independent clinical predictors of loop and thiazide diuretic use using multivariable logistic regression.

We used generalized linear models to compare adjusted levels of mean urinary calcium excretion across the diuretic treatment groups. In addition to total 24-h urinary calcium excretion (mg/day), we analyzed urinary fractional excretion of calcium (FeCa = [urine calcium × serum creatinine]/[serum calcium × urine creatinine] × 100%). The latter corrects for over or under collections of 24-h urine samples and standardizes urinary calcium excretion to the degree of renal dysfunction, which is critical in CKD cohorts in which renal function varies widely. Given known diurnal and postprandial variability in calciuria [22], fractional excretion of calcium was calculated from the 24-h urine specimens rather than spot urine tests. We fit multivariable models using natural log-transformed values to achieve normal distributions and report adjusted means that were back transformed into conventional scale for ease of interpretation.

We used linear and logistic regression to examine the association between PTH levels (log-transformed) and odds of secondary hyperparathyroidism, respectively, according to the diuretic treatment expressed as a categorical variable. Multivariable analyses hierarchically adjusted for case-mix variables [age, gender, race, ethnicity, body mass index (BMI), systolic blood pressure, diabetes mellitus, congestive heart failure, eGFR, clinical center and season of blood draw (October to March compared to other months), laboratory values (serum calcium, phosphate and albumin levels)] and dietary data (protein, sodium, calcium, phosphorus and total calories). We included clinical center as a case-mix covariate to account for differences in clinical practice patterns and sun exposure at the various CRIC centers. We tested for interactions between diuretic class and the clinical characteristics that were independent predictors of choosing a specific diuretic class to determine whether these modified the relationship with PTH levels and odds of secondary hyperparathyroidism. We performed additional analyses to further address potential confounding factors. High sodium intake promotes calciuria [23] and volume expansion, which would be expected to increase diuretic use. Since food

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frequency questionnaires underestimate sodium intake because they do not capture discretionary salt ingestion, we refit the diet-adjusted models after substituting the DHQ estimate of salt intake with 24-h urinary salt excretion as a more precise measure.

Decreased renal function is associated with higher PTH levels, volume expansion and thus a greater likelihood of therapy with loop diuretics. To further address potential confounding factors by differences in renal function that may be misclassified by imprecision in eGFR, we repeated the main analyses after replacing eGFR with creatinine clearance calculated from the 24-h urine collections. We also tested for nonlinear relationships between renal function and secondary hyperparathyroidism by analyzing 10 mL/min/1.73m² increments in eGFR as a categorical variable and by including a quadratic eGFR term. Additionally, to address potential selection bias and confounding by indication, we calculated the propensity scores of likelihood of receiving loop diuretics based on eGFR and other baseline characteristics and then compared PTH levels among loop diuretic users with nonusers stratified by quartiles of propensity score [24].

Phosphate binder, active vitamin D and nutritional vitamin D can lower PTH levels, and the primary indication for vitamin D therapy is an elevated PTH [25]. Therefore, we repeated the main analyses after excluding participants who were treated with these medications, and we adjusted for use of these medications in an additional sensitivity analysis. Because vitamin D deficiency is associated with increased PTH [26], we adjusted for season of baseline blood draw in all participants and adjusted for 25D and 1,25D values in the subset in whom these were available.

Finally, in a prespecified analysis, we tested for interaction between loop and thiazide diuretics to determine whether combined diuretic therapy modified the relationships between monotherapy with PTH levels and secondary hyperparathyroidism. Two-tailed P-values <0.05 were considered statistically significant. We used SAS 9.1 (SAS Institute, Cary, NC) to conduct all analyses.

Results

Characteristics of the study population

Table 1 presents the clinical characteristics of the study population according to the diuretic treatment. Although there were several differences in clinical characteristics between the groups, the strongest independent clinical predictors of treatment with loop diuretics were lower eGFR, history of congestive heart failure, increased BMI and history of diabetes (in descending order of strength of association; Table 2). In contrast, the strongest independent predictors of thiazide treatment were history of hypertension, increasing age and black race (in descending order of strength of association; Table 2). Although serum levels of 25D differed across diuretic groups, there were no significant differences in levels of 1,25D, the active hormonal form of vitamin D that regulates dietary calcium absorption. Estimated dietary intake was similar across the diuretic groups (Table 3) and was not associated with PTH.

Calciumuria

The median 24-h urinary calcium excretion in the overall cohort was 40 (interquartile range: 18–87) mg/day, which is drastically lower than in non-CKD populations (normal range 120–250 mg/day). The independent predictors of a lower 24-h urinary calcium excretion, obtained from adjusted generalized linear models, were lower eGFR, lower urinary salt excretion, higher PTH levels and black race. The Spearman correlation between fractional urinary calcium excretion (which accounts for creatinine excretion) and eGFR was significant (P < 0.001) but weak (R = 0.1). In comparison, the Spearman correlation between 24-h urinary calcium and eGFR was 0.4 (P < 0.001). Among participants treated with diuretics, unadjusted 24-h urinary calcium and fractional excretion of calcium was highest in the loop diuretic group, lowest in the thiazide group and intermediate in the dual therapy group (Table 4). After multivariable adjustment, the loop diuretic group had the highest total 24-h urinary calcium and fractional excretion of calcium, followed by untreated, dual therapy and, finally, the thiazide monotherapy groups (Table 4).

Serum calcium

Compared with the untreated group, the mean crude and multivariable-adjusted serum calcium levels were significantly lower in the loop diuretic group and significantly higher in the thiazide group; mean crude and multivariable-adjusted serum calcium levels in the dual therapy group were intermediate between the monotherapy groups (Table 4).

Diuretics and PTH

Median crude PTH levels were nearly twice as high in the loop diuretic group compared to the untreated group (P < 0.001) but there was no significant difference between the thiazide and untreated groups; PTH levels in the dual therapy group were intermediate between the loop and thiazide monotherapy groups (Figure 1). Loop diuretics were independently associated with increased PTH levels and had significantly higher odds of secondary hyperparathyroidism compared with untreated participants in all multivariable-adjusted models including a series of sensitivity analyses (Table 5). In contrast, thiazides were associated with modestly lower adjusted mean PTH levels compared to untreated participants only in the case-mix-adjusted model [50.0, 95% confidence interval (CI) 47.8–52.3 pg/mL, versus 52.8, 95% CI 51.1–54.6 pg/mL in the untreated group, P = 0.04] and were not associated with lower odds of secondary hyperparathyroidism in any analysis (Table 5).

The relationships between diuretics and PTH levels and odds of secondary hyperparathyroidism were not modified by levels of the main demographic and clinical predictors of diuretic use including age, gender, race, BMI and history of congestive heart failure, hypertension or diabetes. The prevalence of secondary hyperparathyroidism was significantly higher in loop diuretic users versus nonusers in both CKD Stages 2–3 (54 versus 23%) and 4 (81 versus 66%). Adjustment for use of phosphate binders, active vitamin D analogs and nutritional vitamin D did not alter these relationships. In addition, when PTH levels were examined within quartiles of propensity scores of loop diuretic treatment, treated individuals had significantly higher PTH levels than untreated individuals within each quartile (P < 0.05 for all).

Interaction between diuretic classes

In linear regression models of log PTH, there was significant interaction between diuretic treatment groups (unadjusted P for loop × thiazide <0.0001; case-mix adjusted, P = 0.01). The higher adjusted mean PTH in the loop diuretic group was blunted in the loop and thiazide coadministration group (57.2, 95% CI 53.4–61.2 pg/mL, for dual therapy versus 67.9, 95% CI 65.2–70.7 pg/mL for loop monotherapy; P < 0.001). There was also significant interaction between

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Table 1. Characteristics of study participants by diuretic treatmenta

<table>
<thead>
<tr>
<th></th>
<th>Loop diuretics monotherapy</th>
<th>Thiazide diuretics monotherapy</th>
<th>Loop and thiazide dual therapy</th>
<th>No diuretics</th>
<th>N-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59.6 ± 10.0</td>
<td>60.4 ± 9.5</td>
<td>60.8 ± 9.3</td>
<td>55.7 ± 12.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Female</td>
<td>502 (46)</td>
<td>335 (46)</td>
<td>149 (52)</td>
<td>654 (43)</td>
<td>0.03</td>
</tr>
<tr>
<td>Black</td>
<td>574 (53)</td>
<td>351 (49)</td>
<td>148 (51)</td>
<td>502 (33)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hispanic</td>
<td>106 (10)</td>
<td>39 (5)</td>
<td>22 (8)</td>
<td>144 (10)</td>
<td>0.004</td>
</tr>
<tr>
<td>Current smoker</td>
<td>129 (12)</td>
<td>102 (14)</td>
<td>34 (12)</td>
<td>204 (13)</td>
<td>0.41</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>34.3 ± 8.6</td>
<td>31.7 ± 7.5</td>
<td>35.2 ± 7.8</td>
<td>30.2 ± 7.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>134 ± 24</td>
<td>128 ± 21</td>
<td>126 ± 19</td>
<td>124 ± 20</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1013 (93)</td>
<td>692 (96)</td>
<td>278 (96)</td>
<td>1119 (74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>713 (66)</td>
<td>337 (47)</td>
<td>164 (57)</td>
<td>522 (34)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>240 (22)</td>
<td>25 (3)</td>
<td>39 (13)</td>
<td>47 (3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phosphorus binder use</td>
<td>107 (10)</td>
<td>49 (7)</td>
<td>18 (6)</td>
<td>86 (6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium-based binder use</td>
<td>99 (9)</td>
<td>48 (7)</td>
<td>18 (6)</td>
<td>85 (6)</td>
<td>0.005</td>
</tr>
<tr>
<td>Non-calcium-based binder use</td>
<td>10 (0.9)</td>
<td>2 (0.3)</td>
<td>1 (0.3)</td>
<td>1 (0.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>Active vitamin D use</td>
<td>68 (6)</td>
<td>13 (2)</td>
<td>6 (2)</td>
<td>30 (2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Dietary vitamin D supplement use</td>
<td>104 (10)</td>
<td>72 (10)</td>
<td>31 (11)</td>
<td>173 (11)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Laboratory results (serum)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>2.0 ± 0.6</td>
<td>1.6 ± 0.4</td>
<td>1.7 ± 0.6</td>
<td>1.6 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR, mL/min/1.73m²</td>
<td>36.8 ± 11.9</td>
<td>45.5 ± 12.4</td>
<td>42.0 ± 11.8</td>
<td>46.5 ± 13.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.8 ± 0.5</td>
<td>4.1 ± 0.4</td>
<td>3.9 ± 0.5</td>
<td>4.0 ± 0.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>9.1 ± 0.5</td>
<td>9.3 ± 0.5</td>
<td>9.2 ± 0.5</td>
<td>9.2 ± 0.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Phosphate, mg/dL</td>
<td>3.9 ± 0.7</td>
<td>3.7 ± 0.6</td>
<td>3.9 ± 0.8</td>
<td>3.6 ± 0.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D, ng/mLb</td>
<td>17.5 ± 11.0</td>
<td>21.8 ± 10.9</td>
<td>17.2 ± 7.3</td>
<td>23.5 ± 10.7</td>
<td>0.0003</td>
</tr>
<tr>
<td>1,25-Dihydroxyvitamin D, pg/mLb</td>
<td>29.3 ± 10.6</td>
<td>28.6 ± 11.1</td>
<td>26.2 ± 8.4</td>
<td>29.2 ± 9.9</td>
<td>0.5</td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>82 (52–130)</td>
<td>45 (31–74)</td>
<td>57 (37–96)</td>
<td>44 (30–69)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% With secondary hyperparathyroidism</td>
<td>681 (63)</td>
<td>217 (30)</td>
<td>127 (44)</td>
<td>431 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>aValues are N (%), means ± standard deviation.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>b25-Hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were available in 327 and 326 participants, respectively.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Independent predictors of diuretic therapy (N = 3616)a

<table>
<thead>
<tr>
<th>Predictors of loop diuretic therapy</th>
<th>OR 95% CI</th>
<th>χ²</th>
<th>P</th>
<th>Predictors of thiazide diuretic therapy</th>
<th>OR 95% CI</th>
<th>χ²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, per 10 year increase</td>
<td>1.2</td>
<td>1.1–1.3</td>
<td>22.8</td>
<td>&lt;0.001</td>
<td>1.4</td>
<td>1.3–1.5</td>
<td>47.2</td>
</tr>
<tr>
<td>Female sex</td>
<td>0.9</td>
<td>0.7–1.1</td>
<td>1.0</td>
<td>0.31</td>
<td>1.2</td>
<td>0.99–1.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Black race</td>
<td>1.8</td>
<td>1.5–2.3</td>
<td>33.3</td>
<td>&lt;0.001</td>
<td>1.5</td>
<td>1.2–1.9</td>
<td>16.5</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
<td>0.7</td>
<td>0.4–1.1</td>
<td>2.8</td>
<td>0.1</td>
<td>0.8</td>
<td>0.5–0.9</td>
<td>5.1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6.8</td>
<td>4.8–9.6</td>
<td>119.7</td>
<td>&lt;0.001</td>
<td>1.0</td>
<td>0.6–1.7</td>
<td>0.02</td>
</tr>
<tr>
<td>Diabetes</td>
<td>2.3</td>
<td>1.9–2.8</td>
<td>75.1</td>
<td>&lt;0.001</td>
<td>1.5</td>
<td>1.2–1.8</td>
<td>14.6</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.2</td>
<td>1.6–2.9</td>
<td>23.0</td>
<td>&lt;0.001</td>
<td>7.6</td>
<td>5.1–11.4</td>
<td>98.9</td>
</tr>
<tr>
<td>Systolic BP, per 10 mmHg increase</td>
<td>1.1</td>
<td>1.0–1.1</td>
<td>11.9</td>
<td>&lt;0.001</td>
<td>0.96</td>
<td>0.92–1.0</td>
<td>2.3</td>
</tr>
<tr>
<td>BMI, per 1 unit increase</td>
<td>1.1</td>
<td>1.0–1.1</td>
<td>85.8</td>
<td>&lt;0.001</td>
<td>1.02</td>
<td>1.00–1.03</td>
<td>6.1</td>
</tr>
<tr>
<td>eGFR, per 10 mL/min/1.73m² increase</td>
<td>0.61</td>
<td>0.6–0.7</td>
<td>153.4</td>
<td>&lt;0.001</td>
<td>1.1</td>
<td>1.0–1.1</td>
<td>2.8</td>
</tr>
</tbody>
</table>

aThe following covariates were included: age, sex, black race, Hispanic ethnicity, systolic blood pressure, BMI, eGFR, history of congestive heart failure, diabetes or hypertension and clinical center. OR, odds ratio.

Discussion

In this large cohort of CKD patients not yet on dialysis, treatment with loop diuretics was independently associated with higher urinary calcium, lower serum calcium, higher PTH levels and greater odds of secondary hyperparathyroidism compared with no diuretic treatment. Although monotherapy with thiazides was associated with reciprocal changes in calciuria and serum calcium, there was no consistent reduction in PTH levels or odds of secondary hyperparathyroidism compared with untreated patients. However, patients who were treated with both thiazide and loop diuretics had significantly higher serum calcium and lower urinary calcium, PTH levels and odds of secondary hyperparathyroidism than patients treated with loop diuretics alone, suggesting potential protective effects of thiazides in the setting of loop diuretic therapy. Despite the lack of data on the impact of diuretic choice on clinical outcomes, these results are supported by previous studies in the diuretic class and odds of secondary hyperparathyroidism (unadjusted, P < 0.001; case–mix adjusted, P = 0.05) such that the odds ratio of secondary hyperparathyroidism associated with loop diuretic use was blunted in the group that was coadministered thiazides (Figure 2). The latter was driven by CKD Stages 2–3 and not Stage 4 patients (P for loop × thiazide × CKD stage interaction = 0.03; Figure 2).
Established mechanisms of secondary hyperparathyroidism in CKD include hypocalcemia, hyperphosphatemia [27, 28] and calcitriol deficiency caused by increased concentrations of FGF23 [29]. FGF23 normally inhibits PTH secretion, but decreased expression of klotho and FGF receptors in the parathyroid glands in CKD causes resistance to FGF23-mediated PTH suppression [30, 31]. Despite recent advances, the mechanisms underlying why early CKD patients manifest secondary hyperparathyroidism long before they develop abnormal serum calcium or phosphate levels remain unclear [5]. While an increased PTH helps maintain normal serum calcium and phosphate levels in CKD by stimulating bone resorption and phosphaturia and inhibiting calciuria, the mechanisms that stimulate the initial increase in PTH levels are less clear. One important mechanism is negative calcium balance due to impaired dietary calcium absorption caused by deficiency of calcitriol that can be exacerbated by a low calcium intake [32]. These factors are reflected in the progressive reduction in urinary calcium excretion that accompanies declining renal function [32, 33]. Whereas healthy volunteers typically excrete 120–250 mg of calcium daily [34], CKD patients excrete far less, as we observed in the current study (median 40 mg/day).

Patients treated with loop diuretics had significantly lower eGFR and higher PTH compared to all other groups. Since these factors were the primary predictors of low urinary calcium excretion, it would have been expected...
Thiazide diuretics as primary predictor

<table>
<thead>
<tr>
<th>Predictor</th>
<th>N</th>
<th>β</th>
<th>95% CI</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3616</td>
<td>0.56</td>
<td>0.51–0.61</td>
<td>&lt;0.001</td>
<td>4.3</td>
<td>3.6–5.0</td>
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<tr>
<td>Case-mix adjusted</td>
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<td>0.25</td>
<td>0.20–0.30</td>
<td>&lt;0.001</td>
<td>2.1</td>
<td>1.7–2.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine clearance adjusted</td>
<td>3418</td>
<td>0.35</td>
<td>0.30–0.41</td>
<td>&lt;0.001</td>
<td>2.6</td>
<td>2.1–3.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR categories + eGFR adjusted</td>
<td>3592</td>
<td>0.23</td>
<td>0.18–0.28</td>
<td>&lt;0.001</td>
<td>2.1</td>
<td>1.7–2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Linear and quadratic eGFR adjusted</td>
<td>3392</td>
<td>0.23</td>
<td>0.18–0.28</td>
<td>&lt;0.001</td>
<td>2.0</td>
<td>1.7–2.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Laboratory values adjusted</td>
<td>3524</td>
<td>0.23</td>
<td>0.18–0.28</td>
<td>&lt;0.001</td>
<td>1.9</td>
<td>1.6–2.4</td>
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<tr>
<td>Dietary intake adjusted</td>
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<td>0.16–0.28</td>
<td>&lt;0.001</td>
<td>1.9</td>
<td>1.5–2.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Urinary salt excretion adjusted</td>
<td>2589</td>
<td>0.22</td>
<td>0.16–0.28</td>
<td>&lt;0.001</td>
<td>1.9</td>
<td>1.5–2.5</td>
<td>&lt;0.001</td>
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<tr>
<td>Not on vitamin D/binders</td>
<td>2901</td>
<td>0.27</td>
<td>0.21–0.33</td>
<td>&lt;0.001</td>
<td>2.2</td>
<td>1.7–2.8</td>
<td>&lt;0.001</td>
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<tr>
<td>Subsets with 25D level</td>
<td>324</td>
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<td>2.9</td>
<td>1.3–6.5</td>
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</tr>
<tr>
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<tr>
<td>Subsets with 1,25D level</td>
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<td>0.34</td>
<td>0.14–0.54</td>
<td>0.001</td>
<td>3.1</td>
<td>1.4–6.9</td>
<td>0.006</td>
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<tr>
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<td>0.002</td>
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<td>1.1–5.9</td>
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</tr>
</tbody>
</table>

Thiazide diuretics as primary predictor

<table>
<thead>
<tr>
<th>Predictor</th>
<th>N</th>
<th>β</th>
<th>95% CI</th>
<th>P</th>
<th>OR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>3616</td>
<td>0.01</td>
<td>−0.04 to 0.07</td>
<td>0.63</td>
<td>1.1</td>
<td>0.9–1.3</td>
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<tr>
<td>Case-mix adjusted</td>
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<td>−0.11 to −0.001</td>
<td>0.044</td>
<td>0.9</td>
<td>0.7–1.1</td>
<td>0.43</td>
</tr>
<tr>
<td>Creatinine clearance adjusted</td>
<td>3418</td>
<td>−0.04</td>
<td>−0.10 to 0.01</td>
<td>0.12</td>
<td>0.9</td>
<td>0.7–1.2</td>
<td>0.52</td>
</tr>
<tr>
<td>eGFR categories + eGFR adjusted</td>
<td>3592</td>
<td>−0.05</td>
<td>−0.10 to 0.006</td>
<td>0.08</td>
<td>0.9</td>
<td>0.7–1.2</td>
<td>0.50</td>
</tr>
<tr>
<td>Linear and quadratic eGFR adjusted</td>
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<td>−0.10 to 0.004</td>
<td>0.07</td>
<td>0.9</td>
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<td>0.46</td>
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<tr>
<td>Laboratory values adjusted</td>
<td>3524</td>
<td>−0.02</td>
<td>−0.08 to 0.03</td>
<td>0.37</td>
<td>0.96</td>
<td>0.8–1.2</td>
<td>0.78</td>
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<tr>
<td>Dietary intake adjusted</td>
<td>2668</td>
<td>−0.03</td>
<td>−0.09 to 0.03</td>
<td>0.33</td>
<td>0.96</td>
<td>0.7–1.3</td>
<td>0.79</td>
</tr>
<tr>
<td>Urinary salt excretion adjusted</td>
<td>2589</td>
<td>−0.02</td>
<td>−0.09 to 0.03</td>
<td>0.41</td>
<td>0.97</td>
<td>0.7–1.3</td>
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<td>Not on vitamin D/binders</td>
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<td>−0.08 to 0.03</td>
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<td>0.9</td>
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<td>324</td>
<td>0.04</td>
<td>−0.14 to 0.22</td>
<td>0.69</td>
<td>0.98</td>
<td>0.4–2.2</td>
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<td>25D levels adjusted</td>
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<td>−0.16 to 0.18</td>
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<td>0.4–2.1</td>
<td>0.82</td>
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<tr>
<td>Subsets with 1,25D level</td>
<td>323</td>
<td>0.04</td>
<td>−0.14 to 0.22</td>
<td>0.67</td>
<td>1.0</td>
<td>0.4–2.3</td>
<td>0.96</td>
</tr>
<tr>
<td>1,25D levels adjusted</td>
<td>323</td>
<td>0.04</td>
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<td>0.68</td>
<td>0.97</td>
<td>0.4–2.2</td>
<td>0.95</td>
</tr>
</tbody>
</table>

- Users of individual diuretic classes compared to untreated participants.
- Adjusted for age, gender, black race, Hispanic ethnicity, BMI, systolic blood pressure, diabetes, heart failure, eGFR, center and season of blood draw.
- Multivariable adjusted for all factors listed in b with creatinine clearance instead of eGFR.
- Multivariable adjusted for all factors listed in b plus 1,25D levels in those for whom 1,25D levels were available.
- Multivariable adjusted for all factors listed in b but only in those for whom 1,25D levels were available.
- Multivariable adjusted for all factors listed in b plus 25D levels in those for whom 25D levels were available.
- Multivariable adjusted for all factors listed in b but only in those for whom 25D levels were available.
- Multivariable adjusted for all factors listed in b plus 1,25D levels in those for whom 1,25D levels were available.
- OR, odds ratio. sHPT, secondary hyperparathyroidism.

Thiazide diuretics reduce calciuria most likely by enhancing sodium-dependent calcium reabsorption in the proximal tubule rather than via enhanced transport across the distal transient receptor potential cation channel, subfamily V, member 5 [TRPV5], as previously thought [42]. Although thiazide monotherapy was associated with lower levels of calciuria than untreated patients in the current study, it was only marginally associated with modestly lower PTH levels in some but not all analyses. While this might appear to contradict the hypothesis that alterations in calciuria impact PTH levels in CKD, these results are consistent with the observation that calciuria would be lowest in the loop diuretic group. The contrary finding that adjusted urinary calcium excretion was 35% higher in the loop diuretic group compared with the untreated group supports an important direct effect of loop diuretics to increase calciuria and thus PTH that has been reported in other clinical settings [35–39]. Indeed, an established physiological mechanism of action of loop diuretics is to increase calciuria by reducing paracellular calcium reabsorption via directly blocking the sodium–potassium–chloride cotransporter in the thick ascending limb of the renal tubule [39]. In contrast to urinary calcium excretion, neither dietary calcium intake nor calcitriol levels differed by diuretic treatment status. Collectively, these data support the hypothesis that therapy with loop diuretics may exacerbate negative calcium balance in early CKD by inappropriately increasing urinary calcium excretion in the setting of limited dietary calcium absorption [32]. Since loop diuretics are used extensively and for protracted time periods to control volume status in CKD, increased calciuria caused by loop diuretics may represent an important yet underappreciated initiating mechanism of secondary hyperparathyroidism. Indeed, recent comprehensive reviews of diuretics in the general medical and nephrology literature did not even mention their effects on renal calcium handling [40,41]. Thiazide diuretics reduce calciuria most likely by enhancing sodium-dependent calcium reabsorption in the proximal tubule rather than via enhanced transport across the distal transient receptor potential cation channel, subfamily V, member 5 [TRPV5], as previously thought [42]. Although thiazide monotherapy was associated with lower levels of calciuria than untreated patients in the current study, it was only marginally associated with modestly lower PTH levels in some but not all analyses. While this might appear to contradict the hypothesis that alterations in calciuria impact PTH levels in CKD, these results are consistent with the observation that calciuria would be lowest in the loop diuretic group. The contrary finding that adjusted urinary calcium excretion was 35% higher in the loop diuretic group compared with the untreated group supports an important direct effect of loop diuretics to increase calciuria and thus PTH that has been reported in other clinical settings [35–39]. Indeed, an established physiological mechanism of action of loop diuretics is to increase calciuria by reducing paracellular calcium reabsorption via directly blocking the sodium–potassium–chloride cotransporter in the thick ascending limb of the renal tubule [39]. In contrast to urinary calcium excretion, neither dietary calcium intake nor calcitriol levels differed by diuretic treatment status. Collectively, these data support the hypothesis that therapy with loop diuretics may exacerbate negative calcium balance in early CKD by inappropriately increasing urinary calcium excretion in the setting of limited dietary calcium absorption [32]. Since loop diuretics are used extensively and for protracted time periods to control volume status in CKD, increased calciuria caused by loop diuretics may represent an important yet underappreciated initiating mechanism of secondary hyperparathyroidism. Indeed, recent comprehensive reviews of diuretics in the general medical and nephrology literature did not even mention their effects on renal calcium handling [40,41].
sistent with prior studies of osteoporosis prevention in which individuals with normal baseline PTH and urinary calcium excretion who were administered thiazide diuretics experienced a reduction in urinary calcium excretion but no change in PTH [19, 38]. In contrast, coadministration of thiazides and loop diuretics was associated with attenuated urinary calcium losses and lower PTH levels compared with loop diuretics alone, particularly in CKD Stages 2–3 when thiazides retain greater activity in the renal tubules. With no prior published studies regarding the effects on calcium handling of loop and thiazide combination therapy in human or animal models of CKD, we speculate that in the setting of CKD in which calcium was already extremely low, the amount of calcium conservation induced by thiazide monotherapy was too little to induce more than modest reductions in PTH levels that were already in the normal range. However, when cast against a background of inappropriately higher calcium and PTH levels associated with loop diuretics, the physiological relevance of thiazides’ anti-calciuric effects are accentuated, exerting a more pronounced protective effect on calcium balance and thus PTH. Physiological studies should test these hypotheses in detail.

Several limitations and our approach to minimize their impact deserve mention. First, while the cross-sectional design precludes definitive conclusions regarding causality, higher PTH is not an indication for diuretics and the differences in calcium across the diuretic groups conform to known physiological mechanisms. Second, although measurements of vitamin D were only available for a subset of participants, we observed no substantial change in any of the results after adjusting for season of blood draw in the overall cohort or for vitamin D levels in the subset. Furthermore, vitamin D deficiency is associated with decreased urinary calcium excretion [32]. Had vitamin D deficiency been a major confounder of PTH elevation in the loop diuretic group, that group should have had lower rather than higher urinary calcium excretion. Third, dose and duration of diuretic therapy were not available, and thus, we could not evaluate a dose–response effect, which was previously reported outside CKD [36]. Fourth, although we observed significant trends in total serum calcium across the diuretic groups, ionized calcium directly regulates PTH and this was not available. Finally, levels of FGF23 were not available. Since impaired calcitriol-mediated dietary calcium absorption is likely a root cause of our observations and increased FGF23 is the primary mechanism of low calcitriol levels in early CKD [29], the current results could represent an additional indirect manifestation of secondary FGF23 excess in CKD.

Existing treatments for established secondary hyperparathyroidism, such as active forms of vitamin D and calcimimetics, can initially control high PTH levels but become less effective once secondary hyperparathyroidism is firmly established and parathyroid hyperplasia develops. If confirmed, our data suggest novel cost-effective strategies for the primary prevention of secondary hyperparathyroidism. In addition to its many recently publicized benefits [43,44], sodium restriction would be expected to attenuate negative calcium balance in CKD through its known anti-calciuric effects and indirectly by reducing the need for loop diuretics. Second, perhaps thiazide diuretics should be used as a standard therapy to attenuate urinary calcium losses in CKD Stages 2–3 patients in whom loop diuretics are prescribed. Third, treatment with loop diuretics could be considered a novel indication to initiate calcitriol therapy in CKD. By increasing gastrointestinal absorption of calcium, calcitriol could counterbalance increased urinary calcium losses induced by loop diuretics. In the era of comparative effectiveness research, these novel uses of simple, inexpensive and widely available therapeutic modalities should be investigated in longitudinal studies that aim to prevent or delay the onset of secondary hyperparathyroidism and its associated systemic consequences.

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Conflict of interest statement. None declared.


References
Diuretics, calcium and secondary hyperparathyroidism


41. Segura J, Ruijlope LM. Should diuretics always be included as initial antihypertensive management in early-stage CKD? J Clin Invest 2009; 119: 2721–2728


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