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## Association of Loop Diuretic Use With Higher Parathyroid Hormone Levels in Patients With Normal Renal Function

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Elevations in parathyroid hormone (PTH) level have been associated with adverse clinical outcomes, including cardiovascular disease and mortality.<sup>1,2</sup> Loop diuretics have been linked to increased PTH levels in patients with chronic kidney disease (CKD),<sup>3,4</sup> but this association has not been investigated in the general population. We used data from the National Health and Nutrition Examination Survey (NHANES)<sup>5,6</sup> to test the hypothesis that loop diuretic use associates with elevated PTH in adults with preserved renal function.

### Methods

We studied participants from NHANES 2003 to 2004<sup>5</sup> and 2005 to 2006<sup>6</sup> because PTH measurements were available in these years. Participants were excluded for age younger than 18 years, estimated glomerular filtration rate (eGFR) lower than 60 mL/min/1.73 m<sup>2</sup> (using the CKD-EPI [Chronic Kidney Disease Epidemiology Collaboration] equation), or missing PTH value. “Loop users” had prescriptions for furosemide, bumetanide, or torsemide.

Baseline characteristics of loop users and nonusers were compared using *t* tests or  $\chi^2$  tests. A multivariable linear regression model was constructed to test the association between loop use and natural log-transformed PTH level. Covariates were age, sex, body mass index (BMI), history of congestive heart failure (CHF); smoking; dietary calcium and phosphorus

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**Author Contributions:** Dr Corapi had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Corapi, McMahon, Seifter, Bhan.

*Acquisition, analysis, or interpretation of data:* Corapi, McMahon, Wenger, Bhan.

*Drafting of the manuscript:* Corapi, Wenger.

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intake; eGFR; and levels of serum 25-(OH) vitamin D, calcium, phosphorus, uric acid, albumin, and alkaline phosphatase. Least-square means were used to estimate natural log-transformed PTH levels of loop users and nonusers. These values were exponentiated and the adjusted geometric means of PTH level from the final model are reported. Multivariable logistic regression was used to test the association between loop use and odds of a PTH level higher than 65 pg/mL.

## Results

Of 20 470 participants, 9287 were younger than 18 years; 2217 had an eGFR lower than 60 mL/min/1.73 m<sup>2</sup>, and 3 were missing a PTH value. The remaining 8963 participants were included in the analysis. After application of survey weights, 1.8% of participants were loop users.

Loop users were more likely to be female, older, nonsmokers, and have a higher BMI (Table). They had significantly higher uric acid and alkaline phosphatase levels but lower eGFR, 25-(OH) vitamin D, and albumin levels. Loop users had a lower dietary intake of calcium and phosphorus and were more likely to have a history of CHF. Race and serum calcium and phosphorus levels were similar between groups.

The Figure depicts the range of PTH levels among loop users and nonusers. Using the final multivariable model, the adjusted geometric mean PTH level in loop users was significantly higher than in nonusers (43.4 pg/mL compared with 38.8 pg/mL;  $P < .001$ ). Using multivariable logistic regression, loop use was associated with significantly increased odds of a PTH level higher than 65 pg/mL (odds ratio, 1.83 [CI, 1.16–2.88];  $P = .01$ ).

## Discussion

Our results demonstrate that loop use associates with higher PTH, even after adjustment for potential confounders. While previous studies have found similar associations in CKD, we demonstrate that this relationship extends to patients with preserved kidney function, having an impact on a considerably larger population. Clinicians often monitor for electrolyte changes after initiation of loop diuretics but may not measure PTH level. Many loop users are elderly or have CHF, both of which contribute to bone loss. Use of a different diuretic class, repletion of vitamin D, or increased dietary calcium intake may combat a rise in PTH and reduce the risk of adverse outcomes.

## Conclusions

This study included a large, representative sample of adults. Many variables known to influence PTH level were included in the analysis. Missing data limited our ability to examine the relationship between loop use and clinical outcomes, and while we tried to control for potential confounders, residual confounding may exist. Prospective studies are needed to define the direct effect of loop use on PTH level. Nonetheless, our work suggests that loop diuretic use may lead to elevation in PTH level and consequently other adverse clinical effects.

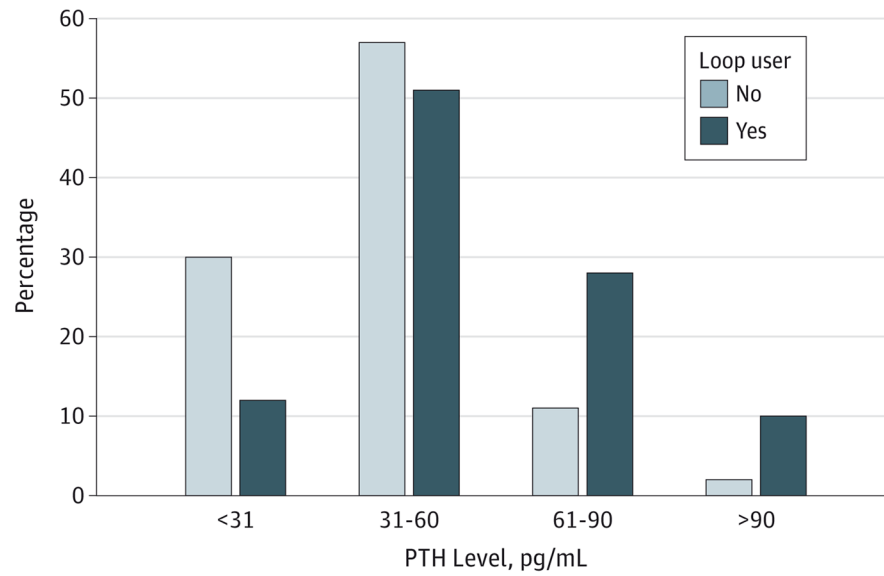
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**Figure. The Range of Parathyroid Hormone (PTH) Levels Among Loop Users and Nonusers**  
Levels are depicted in increments of 30 pg/mL. More loop users have PTH values above the upper limit of normal.

**Table**

Characteristics of Non-Loop Users and Loop Users

Characteristic	Median (Quartiles 1–3)		P Value <sup>a</sup>
	Non-Loop Users (n = 8801)	Loop Users (n = 162)	
Age, y	41.7 (29.9–53.1)	65.7 (55.7–74.9)	<.001
Male, %	48.7	36.4	<.001
African American, %	22.8	25.3	.15
BMI	27.1 (23.7–31.5)	31.4 (27.2–38.7)	<.001
Current smoker, % <sup>b</sup>	21.3	13.6	.01
Hyperparathyroidism, % <sup>c</sup>	6.5	19.8	<.001
History of CHF, %	1.4	32.1	<.001
eGFR, mL/min <sup>d</sup>	96.5 (82.8–109.9)	76.3 (67.6–88.7)	<.001
Calcium level, mg/dL	9.5 (9.3–9.7)	9.4 (9.2–9.6)	.08
Phosphorus level, mg/dL	3.7 (3.4–4.1)	3.7 (3.4–4.1)	.35
Uric acid level, mg/dL	5.2 (4.2–6.1)	5.6 (4.9–6.7)	<.001
Albumin level, g/dL	0.42 (0.40–0.45)	0.40 (0.38–0.42)	<.001
Alkaline phosphatase level, U/L	64.2 (53.1–78.3)	77.1 (65.4–99.3)	<.001
PTH level, pg/mL	37.4 (28.2–49.0)	51.5 (41.3–69.4)	<.001
Total 25 (OH) vitamin D level, ng/mL	22.7 (16.8–28.7)	18.3 (13.1–23.6)	<.001
Dietary calcium level, mg/d	413.1 (268.8–631.3)	330.7 (237.4–511.2)	<.001
Dietary phosphorus level, mg/d	667.4 (473.1–912.8)	515.4 (375.6–705.8)	<.001

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHF, congestive heart failure; CKD, chronic kidney disease; cr, creatinine; eGFR, estimated glomerular filtration rate; EPI, Epidemiology Collaboration; GFR, glomerular filtration rate; PTH, parathyroid hormone.

SI conversion factors: To convert albumin to grams per liter, multiply by 10; to convert alkaline phosphatase to microkatal per liter, multiply by 0.0167; to convert calcium to millimoles per liter, multiply by 0.25; to convert 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.496; to convert uric acid to micromoles per liter, multiply by 59.485.

<sup>a</sup> Bold font indicates statistical significance ( $P < .05$ ).

<sup>b</sup> Defined as having smoked more than 100 cigarettes in one's lifetime and still smoking some or most days of the week.

<sup>c</sup> Defined as PTH level greater than 65 pg/mL.

<sup>d</sup> Calculated using CKD-EPI ( $GFR = 141 \times \min(S_{Cr}/\kappa, 1)^{\alpha} \times \max(S_{Cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018$  [if female]  $\times 1.159$  [if black], where  $S_{Cr}$  indicates serum creatinine and  $\kappa$  is a correction factor, defined as follows:  $\rightarrow 0.7$  if female and  $\rightarrow 0.9$  if male).