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Parathyroid Hormone and the Use of Diuretics and Calcium-Channel Blockers: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Thiazide diuretic (TZ) use is associated with higher bone mineral density, whereas loop diuretic (LD) use is associated with lower bone density and incident fracture. Dihydropyridine-sensitive calcium channels are expressed on parathyroid cells and may play a role in parathyroid hormone (PTH) regulation. The potential for diuretics and calcium-channel blockers (CCBs) to modulate PTH and calcium homeostasis may represent a mechanism by which they influence skeletal outcomes. We hypothesized that the use of LD and dihydropyridine CCBs is associated with higher PTH, and TZ use is associated with lower PTH. We conducted cross-sectional analyses of participants treated for hypertension in the Multi-Ethnic Study of Atherosclerosis who did not have primary hyperparathyroidism or chronic kidney disease ($n=1888$). We used adjusted regression models to evaluate the independent association between TZ, LD, and CCB medication classes and PTH. TZ use was associated with lower PTH when compared with non-TZ use (44.4 versus 46.9 pg/mL, $p=0.02$), whereas the use of LD and CCBs was associated with higher PTH when compared with non-users of each medication class (LD: 60.7 versus 45.5 pg/mL, $p<0.0001$; CCB: 49.5 versus 44.4 pg/mL, $p<0.0001$). Adjusted regression models confirmed independent associations between TZ use and lower PTH ($\beta = -3.2$ pg/mL, $p=0.0007$), and LD or CCB use

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and higher PTH (LD: $\beta = +12.0$ pg/mL, $p < 0.0001$; CCB: $+3.7$ pg/mL, $p < 0.0001$). Among CCB users, the use of dihydropyridines was independently associated with higher PTH ($\beta = +5.0$ pg/mL, $p < 0.0001$), whereas non-dihydropyridine use was not ($\beta = +0.58$ pg/mL, $p = 0.68$). We conclude that in a large community-based cohort with normal kidney function, TZ use is associated with lower PTH, whereas LD and dihydropyridine CCB use is associated with higher PTH. These associations may provide a mechanistic explanation linking use of these medications to the development of skeletal outcomes.

Keywords

PARATHYROID HORMONE; PARATHYROID; HYPERTENSION; DIURETICS; CALCIUM-CHANNEL BLOCKERS; EPIDEMIOLOGY

Introduction

Parathyroid hormone (PTH) plays an important role in calcium and skeletal homeostasis. Prior studies have shown that having both hypertension and the use of antihypertensive medications may influence skeletal health and parathyroid function.^(1–4) In this regard, loop diuretic use is associated with a decrease in bone mineral density⁽⁵⁾ and increased fracture risk with long-term use.^(6,7) In contrast, the use of thiazide diuretics is associated with more favorable skeletal outcomes, including a decrease in cortical bone loss,^(8,9) increased bone mineral density (BMD),⁽¹⁰⁾ and a reduction in fracture risk.^(11,12) On the other hand, calcium-channel blockers have shown mixed effects on bone mineral density and fracture outcomes, likely because of the heterogeneous nature of the medication class, which is subdivided into dihydropyridine and non-dihydropyridine subclasses. For example, amlodipine (a dihydropyridine) use has been shown to preserve bone density in rats,⁽¹³⁾ whereas in humans, chronic nifedipine use (a dihydropyridine) did not change bone metabolism in men.⁽¹⁴⁾ The use of calcium-channel blockers has been associated with a reduced risk of fracture; however, it is the use of non-dihydropyridine calcium-channel blockers that appears to drive this observation.⁽¹⁵⁾

In those with chronic kidney disease (CKD), the use of loop diuretics has been associated with higher PTH levels,⁽¹⁶⁾ whereas in individuals without CKD, loop diuretics have been associated with a higher risk of developing primary hyperparathyroidism.⁽¹⁾ Notably, human parathyroid cells express dihydropyridine-sensitive L-type calcium channels^(17,18) involved in calcium signaling,⁽¹⁹⁾ and calcium-channel blockers in general have been associated with inconsistent modulations of PTH in human interventional studies.^(14,20–23)

Given how frequently these medications are used, and because the aforementioned associations may influence skeletal integrity and the risk for fracture, understanding how these antihypertensive medications may modulate PTH levels has public health relevance. We hypothesized that use of thiazide diuretics could lower PTH levels and use of loop diuretics and calcium-channel blockers (specifically the dihydropyridine class of calcium-channel blockers) could raise PTH levels. We tested these hypotheses by conducting a cross-sectional study to examine the independent association between each of these antihypertensive medication classes and PTH levels in a large community-based cohort of

hypertensive participants without chronic kidney disease or apparent primary hyperparathyroidism.

Materials and Methods

Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a prospective cohort study of 6814 community-living adults aged 45 to 84 years, which was established to study subclinical cardiovascular disease risk factors.⁽²⁴⁾ Subjects without cardiovascular disease were recruited from six centers across the US (New York, NY; Baltimore, MD; Forsyth County, NC; Chicago, IL; St. Paul, MN; and Los Angeles, CA). Institutional board review approved the study at all sites, and participants provided informed consent. Further details of the study have been described previously.⁽²⁴⁾

For the current analysis, data from the baseline examination was used, which was conducted over a 24-month period from 2000 to 2002, and included demographic variables, laboratory data, and medication reporting. Of the 6814 participants, we restricted our analyses to only those using antihypertensive medications for the indication of hypertension because hypertension in itself is known to influence parathyroid function and is associated with higher PTH levels^(1,2) (Supplemental Fig. S1). We excluded those with missing PTH values and those with potentially unrecognized primary hyperparathyroidism (Ca >10.2 mg/dL and PTH >65 pg/mL). To restrict our investigation to a population without secondary hyperparathyroidism due to chronic kidney disease, we also excluded those with an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² (Supplemental Fig. S1).

Assessment of demographic variables

All demographic, historical, and laboratory data used were collected at the baseline examination 1, during years 2000 to 2002. Questionnaires and standardized interviews administered by study coordinators were completed by all participants in order to obtain demographic, medical history, and medication use data.

Assessment of antihypertensive medication use

Antihypertensive medication use was determined by a medication inventory approach.⁽²⁵⁾ Participants were asked to bring all of their medication containers for medications used during the 2 weeks before the visit. The study interviewer recorded the name of each medication, the prescribed dose, and the frequency of administration directly from the containers. Participants were also asked about how many pills they had taken over the past 2 weeks on average per day/week/month. Antihypertensive medication use was categorized by drug class to include thiazide diuretics, loop diuretics, calcium-channel blockers, renin-angiotensin-aldosterone system inhibitors, beta-blockers, and alpha-blockers. Calcium-channel blockers were further subclassified into dihydropyridines (amlodipine or nifedipine) and non-dihydropyridines (verapamil or diltiazem).

Laboratory measurements

All serum and urine samples were collected after an overnight fast, in the morning before 10 a.m. and stored at -80°C before analysis. Intact serum PTH concentrations were measured at the University of Washington using the Beckman-Coulter Dx1 automated two-site immunoassay (Beckman-Coulter, Inc., Brea, CA, USA). Between-lot variations in PTH were adjusted using repeated measurements of aliquoted serum samples from 20 normal controls. The resulting interassay coefficient of variation was 6.1% at 30.1 pg/mL and 3.4% at 94.5 pg/mL, comparable to other validated PTH assays.⁽²⁶⁾ Annualized mean 25OHD concentrations were estimated from single 25OHD measurements as previously described.⁽²⁷⁾ Serum creatinine was used to estimate eGFR by the CKD-EPI equation.⁽²⁸⁾ Serum and urinary calcium, serum and urinary phosphorous, and FGF-23 were all measured as previously described.⁽²⁹⁾

Statistical analysis

To evaluate the univariate associations between each medication and PTH, we first conducted *t* tests comparing mean PTH levels among users of each medication class (thiazides, loop diuretics, and calcium-channel blockers) to non-users of each medication class. Non-users of each medication class were by definition hypertensives using at least one or more other antihypertensive medication. We then used multivariable linear regression to examine the association between each individual medication class (thiazides, loop diuretics, and calcium-channel blockers) and PTH. Medication use was categorized as yes/no; therein, each categorical medication variable permitted comparison between users of that medication with all non-users of that medication that were using other antihypertensives. We adjusted for known and potential confounders of PTH in our regression models. Model A included adjustment for age, race, sex, body-mass index (BMI), eGFR, 25OHD, diabetes status (defined as normal, impaired fasting glucose, or diabetes based on the 2003 American Diabetes Association fasting criteria), smoking history (never, former, current), level of education (no schooling through grade 11, or completed high school/GED through some college completed, or technical school certificate through graduate/professional school degree), and physical activity (reported physical activity hours per week). Model B included adjustment for variables in model A plus systolic blood pressure and use of other antihypertensive medications (thiazides, loop diuretics, calcium-channel blockers, renin-angiotensin-aldosterone system inhibitors, beta-blockers, and alpha-blockers) in order to reduce confounding by other antihypertensive medication use. Model C was an exploratory model that included adjustment for variables in models A and B, as well as for biochemical parameters that may be responsible for influencing PTH: serum calcium, serum phosphate, urinary calcium-creatinine ratio, urinary phosphate-creatinine ratio, and serum fibroblast growth factor 23 (FGF-23). We considered model C to be exploratory because many of the biochemical parameters included as confounders in this model may actually be physiologic intermediates in the relationship between the antihypertensive medication classes of interest and PTH levels.

We used logistic regression to assess the odds of having a PTH level greater than the upper limit of the reference range (>65 pg/mL) for each antihypertensive medication class. In addition, we performed adjusted linear regression analyses after assigning treated

hypertensives who used neither thiazides, loop diuretics, nor calcium-channel blockers (ie, users of RAAS inhibitors, beta-blockers, and/or alpha-blockers only) as the collective reference group. This referent group was chosen in order to interpret the magnitude of association effect between our antihypertensive classes of interest against a single and constant referent category. This model was adjusted for age, race, sex, BMI, eGFR, 25OHD, diabetes status, systolic blood pressure, education level, cigarette smoking, activity level, serum calcium, serum phosphate, urinary calcium-creatinine ratio, urinary phosphate-creatinine ratio, and serum FGF-23. We further restricted this analyses to participants using only a single antihypertensive medication ($n=1167$), given the concern for confounding by use of multiple medications in the cohort.

SAS version 9.3 (SAS Institute, Cary, NC, USA) statistical software was used for all analyses. A two-tailed p value <0.05 was used to indicate statistical significance.

Results

Study population

The mean age of the study population was 64.1 years, with 54.5% being women, and with a mean BMI of 29.7 kg/m² (Table 1). The mean PTH concentration was 46.1 pg/mL (standard deviation [SD] 19.3 pg/mL), mean 25OHD of 24.6 ng/mL (SD 12.2 ng/mL), and the mean eGFR was 79.9 mL/min/1.73 m² (SD 13.0 mL/min/1.73m²). The majority of the study population (61.8%) used only a single antihypertensive medication (Table 1).

Mean PTH levels with diuretic and calcium-channel blocker use

There were 518 participants who used thiazide diuretics, 82 participants who used loop diuretics, and 637 participants who used calcium-channel blockers. Among calcium-channel blocker (CCB) users, 448 participants used dihydropyridines and 189 used non-dihydropyridines (Table 2). Participants using thiazide diuretics had lower PTH levels, higher serum calcium levels, and a lower urine calcium/creatinine ratio, when compared with non-users of thiazides (Table 2). Loop-diuretic users had higher PTH levels, as well as lower serum calcium and higher urine calcium/creatinine ratio, when compared with non-users of loop diuretics (Table 2). The use of any calcium-channel blocker was associated with higher PTH levels and a higher urine calcium/creatinine ratio when compared with non-users of calcium-channel blockers. However, this difference appeared to be driven by the subclass of calcium-channel blocker used. Users of dihydropyridines had a higher PTH, lower serum calcium, and higher urinary calcium/creatinine ratio, whereas the use of non-dihydropyridines was not associated with any difference in PTH when compared with non-users. The percent of participants using each medication class who had a PTH value greater than the upper limit of the reference range paralleled the aforementioned trends (Table 2).

Independent associations between PTH and use of diuretics and calcium-channel blockers

The independent association between diuretic and calcium-channel blocker medications and PTH concentrations were evaluated using adjusted regression models. Thiazide diuretics were associated with lower PTH levels (-3.2 pg/mL [$-5.1, -1.4$], $p=0.0007$), whereas loop diuretics ($+12.0$ pg/mL [$8.1, 16.0$], $p<0.0001$) and calcium-channel blockers ($+3.7$ pg/mL

[1.9, 5.4], $p < 0.0001$) were associated with higher PTH levels (Table 3). The effect estimates of these relationships remained stable and significant after adjustment for variables in models A and B, which included known and potential confounders including demographic variables, systolic blood pressure, kidney function and vitamin D levels, and use of other antihypertensive medications (Table 3). Further adjustment with biochemical measurements known to influence PTH that are changed by diuretics in model C did not appreciably change the effect sizes (Table 3).

PTH and the use of specific calcium-channel blocker subclasses

We repeated our regression models after subclassifying calcium channel blockers as dihydropyridines or non-dihydropyridines. Adjusted models revealed a positive and significant association between use of dihydropyridine calcium-channel blockers and PTH (+5.0 pg/mL [3.0, 6.9], $p < 0.0001$), whereas non-dihydropyridine use was not associated with any significant difference in PTH (Table 4).

Medication classes and the odds of having a PTH value > 65 pg/mL

We used logistic regression to evaluate the odds of having a PTH level greater than the upper limit of the reference range (>65 pg/mL) for diuretics and calcium-channel blockers. Thiazide use was associated with having a PTH within the reference range, whereas the use of loop diuretics and dihydropyridine calcium-channel blockers was associated with higher odds for having a PTH greater than the reference range (Supplemental Table S1).

Non-users of diuretics and calcium-channel blockers as the reference group

To compare the effect estimates of diuretic and calcium-channel blocker use to a uniform reference group, we conducted additional regression models after assigning non-users of thiazides, loop diuretics, and calcium-channel blockers as the reference category. We again observed the same pattern; both loop-diuretic and dihydropyridine CCB use were associated with higher PTH levels, whereas thiazide use was associated with lower PTH levels. Non-dihydropyridine CCB use was not associated with a significant difference in PTH levels (Supplemental Table S2). We further restricted this analyses to those using only a single antihypertensive medication ($n = 1167$) to ensure the multivariable regression results were not confounded by use of multiple antihypertensive medications. In this smaller and restricted analysis, we observed a relative recapitulation of our findings in the total study population (Supplemental Table S2). Comparisons between users of these medications and untreated hypertensives are presented graphically in Fig. 1 and demonstrate a similar trend found in above analyses.

Discussion

Antihypertensive medication use has been associated with skeletal and parathyroid outcomes, including changes in BMD, risk for fracture, and risk for developing primary hyperparathyroidism; however, the mechanisms between these exposures and outcomes have not been well investigated. We hypothesized that individual antihypertensive medication classes may modulate PTH and that the direction of these effects may provide some insight into prior links between antihypertensive medication use and skeletal outcomes. Herein, we

conducted a cross-sectional study in a large community-living sample of individuals without renal disease or overt primary hyperparathyroidism and observed that the use of loop diuretics and dihydropyridine calcium-channel blockers was associated with higher PTH levels (approximately +12 pg/mL and +5 pg/mL, respectively), and the use of a thiazide diuretic was associated with lower PTH levels (approximately -3 pg/mL), when compared with participants not using these medications. These observations were independent of many potential confounders and remained consistent in more stringent subanalyses.

Many prior studies have shown links between diuretics and skeletal outcomes. Loop diuretics are associated with decreases in BMD⁽⁶⁾ and with an increased risk for fracture.⁽⁷⁾ An indication that the link between loop diuretics and these skeletal events may be mediated by PTH is suggested in prior prospective studies that showed the use of loop diuretics associated with an increased risk for developing primary hyperparathyroidism.⁽¹⁾ Loop diuretics can indirectly stimulate PTH secretion by increasing calciuria (potentially inducing a negative calcium balance), which may cause chronic parathyroid stimulation. Indeed, the maintenance of a very low calcium intake has been shown to increase the risk of primary hyperparathyroidism.⁽³⁰⁾ However, a recent study suggests that loop diuretics may also be capable of directly stimulating PTH secretion, independent from calciuric effects, via loop diuretic-responsive NKCC1 receptors in parathyroid tissue.⁽³¹⁾ Our observation of higher PTH levels with loop diuretics is echoed by studies in cohorts with chronic kidney disease who have higher PTH levels⁽¹⁶⁾ and more recently in a cohort without kidney disease.⁽³²⁾ Thiazides decrease calciuria (potentially inducing positive calcium balance) and have been shown to increase bone density and are associated with a lower risk for fracture.⁽³³⁾ The few interventional studies that evaluated PTH levels have shown a trend toward lower PTH levels;^(8,10,33) however, these may have been underpowered to find a statistically significant effect. In contrast, our study, with a large sample size of thiazide users among users of other antihypertensives, was able to detect a significantly lower PTH.

Few studies have evaluated whether calcium-channel blockers have any impact on skeletal health; however, studies have suggested that they may associate with a decreased rate of fracture⁽¹⁵⁾ and that L-type voltage gated calcium channels are expressed on parathyroid tissue.^(18,19) To our knowledge, there are no randomized studies evaluating the effect of calcium-channel blockers on skeletal or parathyroid outcomes. Small interventional studies evaluating for a possible calcimimetic effect of calcium-channel blockers have yielded inconsistent results; some studies have shown that CCBs (diltiazem,⁽²⁰⁾ nifedipine⁽³⁴⁾) may lower PTH, raise PTH (diltiazem,⁽²³⁾ nifedipine⁽²²⁾), or have no effect on PTH (diltiazem,⁽²¹⁾ nicardipine,⁽³⁵⁾ nifedipine⁽¹⁴⁾). Many of these studies focused on diltiazem (a non-dihydropyridine calcium-channel blocker), as well as older, less commonly prescribed dihydropyridine calcium-channel blockers such as nifedipine and nicardipine. Our analyses included amlodipine, a relatively newer and more widely prescribed dihydropyridine calcium-channel blocker for essential hypertension. We found a significant disparity between the association of dihydropyridine and non-dihydropyridine calcium-channel blockers with PTH; dihydropyridine calcium-channel blocker use was associated with a significantly higher PTH than non-users, whereas non-dihydropyridine use did not display any association with PTH concentrations. Our findings also demonstrate that dihydropyridine calcium-channel blocker use was associated with significantly higher

urinary calcium excretion, similar to loop-diuretic use, whereas non-dihydropyridine calcium-channel blocker use was not associated with significant differences in calciuria.

Although our analyses was not specifically designed to investigate how individual medications could cause these associations with PTH, there are at least three potential mechanisms to consider as possible explanations for our results: 1) increasing or decreasing calciuria leading to compensatory changes in PTH; 2) a direct stimulation of the parathyroid glands; and/or 3) volume depletion with loop diuretics resulting in enhanced renin-angiotensin-aldosterone system activity, which can increase PTH secretion. Renal calcium handling is a noteworthy consideration because we observed that loop diuretic users had significantly lower serum calcium and higher urinary calcium-creatinine ratio, and the inverse finding with thiazide use. The accompanying higher and lower PTH levels may, therefore, be a consequence of these renal effects. Our observation that dihydropyridine, but not non-dihydropyridine, calcium-channel blockers displayed a pattern of serum and urinary calcium as well as PTH levels similar to loop diuretics is unique. Dihydropyridines do not have a well-described hypercalciuric effect but may in fact be inducing a mild hypercalciuria that induces a secondary PTH hypersecretion. In this regard, future studies should consider whether specifically dihydropyridine calcium-channel blockers influence renal calcium handling and subsequent skeletal outcomes. Some studies have provided support for a direct stimulatory effect on parathyroid tissue by antihypertensive agents. Even after adjustment for serum and urinary calcium and phosphorous, the association of antihypertensive medications with PTH did not appreciably change. It may be that one-time measurement of these electrolytes did not fully capture time-averaged levels and, therefore, did not fully attenuate the components of the pathway leading to changes in PTH through calcium and phosphate. However, this finding also raises the possibility of mechanisms independent from a compensatory PTH response reactive to electrolyte changes. Recent studies have shown that dihydropyridine L-type calcium channels, loop-diuretic-responsive NKCC1 receptors, and angiotensin type 1 and mineralocorticoid receptors are all present in parathyroid tissue.^(19,31,36)

Strengths and limitations

Our study had a large sample size, with comprehensive and systematically collected demographic and laboratory variables. We were able to recapitulate our findings even after restricting the study population to hypertensive participants using only a single antihypertensive medication, thereby reducing confounding attributable to multiple medication use. Further, all of our findings were robust and stable after extensive multivariable adjustments. Our study also has important limitations. Given the cross-sectional nature of this study, we cannot comment on temporal relationships between antihypertensive medication use and PTH. The cumulative and chronic duration of medication use was not assessed; participants were only confirmed to have taken the antihypertensive medications for 2 weeks before the assessment. Because we restricted our study population to hypertensive participants without CKD, the number of participants using loop diuretics was relatively low ($n=82$); however, the statistical significance of our findings remained robust even with this limitation. We lacked information regarding dietary calcium and vitamin D supplementation, which are known to influence PTH; however, given that all

laboratory collection was performed while fasting, the acute effect of calcium intake on PTH is expected to be minimal. All measurements were made at one point in time, thus we do not have the ability to determine diurnal changes or changes over time within individuals. In addition, we did not have measures of ionized calcium, and the serum calcium levels used in our models were not corrected for serum albumin.

Lastly, we acknowledge that the reference group in our main analyses differed by each antihypertensive medication class; this makes comparison of the magnitude of effect estimates between classes challenging. However, we showed that the directionality and relative magnitude of our effect estimates remained consistent when we conducted an analyses whereby we assigned a consistent reference group of all non-users of diuretics and CCBs (reference group used only RAAS inhibitors, beta-blockers, and alpha-blockers).

In summary, we observed that the use of loop diuretics and dihydropyridine calcium-channel blockers was independently associated with higher PTH levels and that use of thiazide diuretics was independently associated with lower PTH levels. Whether these findings may explain prior observations of skeletal outcomes associated with the use of these antihypertensive medications and implicate PTH regulation as a possible mechanism for these observations warrants further study. Future studies to evaluate whether dihydropyridine calcium-channel blockers increase calciuria and negatively impact skeletal health may provide further insights. How these observations could impact the selection of antihypertensive medications in patients at higher risk for adverse skeletal and parathyroid outcomes also warrants further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors' roles: SZ, AV, and JB developed the study concept and design, performed the statistical analyses, drafted the manuscript, and take responsibility for the data integrity. IB, MA, BP, CR, JI, BK, and DS participated in the study design, reviewed and interpreted the data, and drafted the manuscript.

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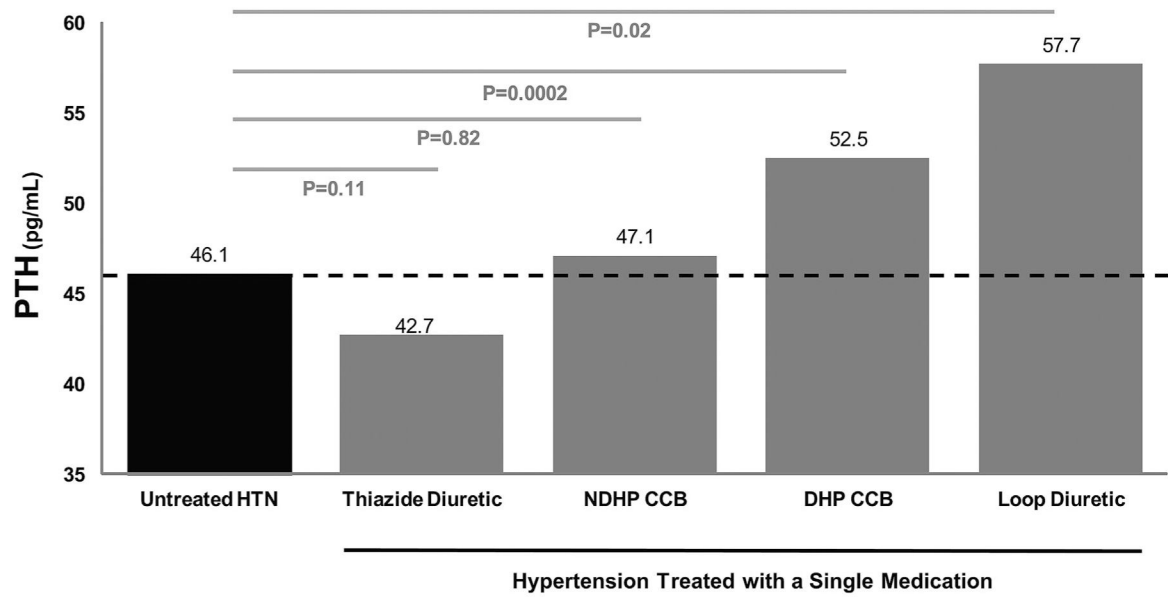


Fig. 1. Mean PTH concentrations among hypertensive participants taking only one single antihypertensive medication (gray bars), compared with untreated hypertensives (black bar). PTH =parathyroid hormone; HTN =hypertension; NDHP =non-dihydropyridine; CCB =calcium-channel blocker; DHP =dihydropyridine.

Table 1**Demographic and Biochemical Characteristics of the Study Population**

Characteristic	N =1888
Age (years)	64.1 (9.2)
Female (no. [%])	1029 (54.5)
Race/ethnicity (no. [%])	
White	616 (32.6)
Chinese-American	170 (9.0)
African-American	731 (38.7)
Hispanic	371 (19.7)
BMI (kg/m ²)	29.7 (5.7)
Systolic blood pressure (mmHg)	133.8 (21.4)
Diastolic blood pressure (mmHg)	73.9 (10.5)
Antihypertensive medications (no. [%])	
Thiazide	518 (27.4)
Loop diuretic	82 (4.3)
Calcium-channel blocker	637 (33.7)
Dihydropyridine CCB	448 (23.7)
Non-dihydropyridine CCB	189 (10)
Beta-blocker	472 (25)
RAAS-inhibitor	891 (47.2)
Alpha-blocker	194 (10.3)
No. of antihypertensive medications	
1	1167 (61.8)
2	523 (27.7)
3	158 (8.4)
3+	26 (1.4)
Education (highest level completed) (no. [%])	
No schooling to some high school	353 (18.8)
Completed high school to some college	690 (36.7)
Completed post-secondary school degree	838 (44.6)
Smoking status (no. [%])	
Never smoker	925 (49.2)
Former	741 (39.4)
Current	215 (11.4)
Physical activity (mean hr/d)	12.4 (6.1)
Diabetes status (no. [%])	
Normal	1178 (32.4)
Impaired fasting glucose	308 (16.3)
Diabetes	402 (21.3)
PTH (pg/mL)	46.1 (19.3)
eGFR (mL/min/1.73m ²)	79.9 (13.0)

Characteristic	N =1888
Serum calcium (mg/dL)	9.65 (0.38)
Urine calcium/Cr ratio (mg/g)	0.09 (0.07)
Serum phosphate (mg/dL)	3.6 (0.5)
Urine phosphate/Cr ratio (mg/g)	0.48 (0.2)
Annualized 25OHD (ng/mL)	24.6 (11.2)
FGF23 (pg/mL)	40.4 (18.9)

Values are mean (SD) unless otherwise specified.

BMI =body mass index; CCB =calcium-channel blocker; PTH =parathyroid hormone; eGFR =estimated glomerular filtration rate; Cr =creatinine; 25OHD =25-hydroxyvitamin D; FGF-23 =fibroblast growth factor 23.

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Table 2

Relevant Characteristics by Individual Antihypertensive Class

Characteristic	Thiazide		Loop diuretic		CCB		Dihydropyridine-CCB		Non-dihydropyridine-CCB	
	Y (n =518)	N (n =1370)	Y (n =82)	N (n = 1806)	Y (n =637)	N (n =1251)	Y (n =448)	N (n =1440)	Y (n =189)	N (n =1699)
Age (years)	63.8 (9.3)	64.3 (9.2)	65.0 (8.4)	64.1 (9.2)	64.6 (9.0)	63.9 (9.3)	64.5 (9.1)	64.0 (9.3)	64.9 (9.0)	64.0 (9.2)
Female (no. [%])	330 (63.7)***	699 (51.0)	57 (69.5)**	972 (53.8)	357 (56.0)	672 (53.7)	238 (53.1)	791 (54.9)	119 (63.0)*	910 (53.6)
Ethnicity (no. [%])										
White	173 (33.4)	443 (32.3)	27 (32.9)	589 (32.6)	145 (22.8)***	471 (37.7)	94 (21.0)***	522 (36.3)	51 (27.0)	565 (33.3)
Chinese-American	17 (3.3)***	153 (11.2)	2 (2.4)*	168 (9.3)	58 (9.1)	112 (9.0)	50 (11.2)	120 (8.3)	8 (4.2)*	162 (9.5)
African-American	260 (50.2)***	471 (34.4)	35 (42.7)	696 (38.5)	314 (49.3)***	417 (33.3)	217 (48.4)***	514 (35.7)	97 (51.3)***	634 (37.3)
Hispanic	68 (13.1)***	303(22.1)	18 (22.0)	353 (19.6)	120 (18.8)	251 (20.1)	87 (19.4)	284 (19.7)	33 (17.5)	338 (19.9)
BMI (kg/m ²)	30.7 (5.9)***	29.4 (5.6)	34.5 (7.6)***	29.5 (5.5)	29.9 (5.8)	29.6 (5.6)	29.8 (5.8)	29.7 (5.7)	30.3 (5.9)	29.7 (5.7)
Systolic blood pressure (mmHg)	133.0 (18.7)	134.2 (22.4)	132.8 (22.6)	133.9 (21.4)	135.4 (19.3)*	133.0 (22.4)	134.6 (19.8)	133.6 (21.9)	137.5 (17.9)*	133.4 (21.8)
Diastolic blood pressure (mmHg)	73.1 (10.2)	74.2 (10.6)	68.9 (10.3)	74.1 (10.4)	74.6 (9.7)	73.5 (10.8)	74.9 (9.7)	73.6 (10.7)	74.2 (9.7)	73.9 (10.6)
PTH (pg/mL)	44.4 (18.5)*	46.8 (19.5)	60.7 (22.4)***	45.5 (18.9)	49.5 (20.9)***	44.4 (18.2)	50.4 (20.8)***	44.8 (18.6)	47.5 (21.3)	46.0 (19.1)
PTH >65 pg/mL (%)	10.8	13.9	29.3***	12.3	17.6***	10.7	19.4***	11.0	13.2	13.0
eGFR (mL/min/1.73m ²)	79.0 (12.3)*	80.3 (13.3)	80.1 (12.3)	79.9 (13.0)	81.3 (13.1)**	79.3 (12.9)	81.6 (13.4)**	79.4 (12.8)	80.6 (12.1)	79.9 (13.1)
Serum calcium, (mg/dL)	9.7 (0.4)**	9.6 (0.4)	9.6 (0.36)*	9.7 (0.38)	9.6 (0.4)	9.7 (0.4)	9.6 (0.4)	9.7 (0.4)	9.6 (0.4)	9.7 (0.4)
Urine calcium/Cr ratio (mg/g)	0.07 (0.08)***	0.10 (0.06)	0.13 (0.1)***	0.09 (0.07)	0.11 (0.1)**	0.09 (0.07)	0.11 (0.1)***	0.09 (0.07)	0.11 (0.08)*	0.09 (0.07)
Serum phosphate (mg/dL)	3.7 (0.5)*	3.6 (0.5)	3.7 (0.5)	3.6 (0.5)	3.6 (0.5)**	3.7 (0.5)	3.6 (0.5)*	3.7 (0.5)	3.6 (0.5)	3.7 (0.5)
Urine phosphate/Cr ratio (mg/g)	0.47 (0.5)	0.48 (0.5)	0.54 (0.2)**	0.48 (0.2)	0.47 (0.2)	0.48 (0.2)	0.49 (0.2)	0.48 (0.2)	0.43 (0.2)**	0.48 (0.2)
Annualized 25(OH)D (ng/mL)	23.3 (10.0)**	25.1 (11.6)	22.0 (10.6)*	24.7 (11.2)	24.0 (13.1)	24.9 (10.1)	24.6 (14.0)	24.6 (10.1)	22.7 (10.4)*	24.8 (11.3)
FGF23 (pg/dL)	41.3 (14.5)	40.0 (20.3)	41.5 (12.2)	40.3 (19.1)	40.0 (25.4)	40.6 (14.4)	38.9 (13.2)	40.8 (20.3)	42.7 (42.0)	40.12 (14.1)

Values are mean (SD) unless otherwise specified.

Y =user of medication in question; N =non-user of medication in question; CCB =calcium-channel blocker; BMI =body mass index; PTH =parathyroid hormone; eGFR =estimated glomerular filtration rate; Cr =creatinine; 25(OH)D, 25hydroxyvitamin D; FGF-23 =fibroblast growth factor 23.

* $p < 0.05$

** $p < 0.01$

$p < 0.0001$

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Table 3
 The Association (With 95% Confidence Intervals) Between Antihypertensive Medication Class and PTH Level

Model	Thiazide		Loop Diuretic		CCB	
	β (95% CI)	p value	β (95% CI)	p value	β (95% CI)	p value
Univariate	-2.3 (-4.3, -0.4)	0.02	+15.2 (11.0, 19.4)	<0.0001	+5.1 (3.3, 7.0)	<0.0001
Multivariate A	-4.2 (-6.1, -2.3)	<0.0001	+12.2 (8.1, 16.3)	<0.0001	+4.3 (2.6, 6.1)	<0.0001
Multivariate B	-3.3 (-5.2, -1.4)	0.0007	+11.4 (7.3, 15.4)	<0.0001	+3.7 (1.9, 5.5)	<0.0001
Multivariate C	-3.2 (-5.1, -1.4)	0.0007	+12.0 (8.1, 16.0)	<0.0001	+3.7 (1.9, 5.4)	<0.0001

PTH =parathyroid hormone; CCB =calcium-channel blocker.

Units for β are pg/mL of PTH per use of antihypertensive drug.

Multivariate A: adjusted for age, ethnicity, sex, body mass index (BMI), vitamin D25OH, estimated glomerular filtration rate (eGFR), diabetes status, education level, cigarette smoking, and physical activity.

Multivariate B: adjusted for age, ethnicity, sex, BMI, vitamin D25OH, eGFR, systolic blood pressure, diabetes status, education level, cigarette smoking, physical activity, and other antihypertensive medication use (HCTZ: adjusted for use of loop diuretics, calcium-channel blockers, RAAS-inhibitor, beta-blocker, and alpha-blocker use; loop diuretics: adjusted for use of thiazide, calcium-channel blockers, RAAS-inhibitor, beta-blocker, and alpha-blocker use; CCB: adjusted for use of thiazide, loop diuretics, RAAS-inhibitor, beta-blocker, and alpha-blocker use).

Multivariate C: adjusted for age, ethnicity, sex, BMI, vitamin D25OH, eGFR, systolic blood pressure, diabetes status, education level, cigarette smoking, physical activity, other antihypertensive medication class use, serum calcium, serum phosphate, urinary calcium/cr, urinary phosphate/cr, and FGF-23.

Table 4

The Association (With 95% Confidence Intervals) Between Calcium-Channel Blocker Subclasses and PTH Level

Model	Dihydropyridine-CCB		Non-dihydropyridine-CCB	
	β (95% CI)	<i>p</i> value	β (95% CI)	<i>p</i> value
Univariate	+5.6 (3.6, 7.6)	<0.0001	+1.49 (-1.4, 4.4)	0.31
Multivariate A	+5.6 (3.6, 7.5)	<0.0001	-0.54 (-3.3, 2.2)	0.50
Multivariate B	+5.2 (3.2, 7.2)	<0.0001	+0.27 (-2.5, 3.1)	0.85
Multivariate C	+5.0 (3.0, 6.9)	<0.0001	+0.58 (-2.1, 3.3)	0.68

PTH =parathyroid hormone; CCB =calcium-channel blocker.

Units for β are pg/mL of PTH per use of antihypertensive drug.

Multivariate A: adjusted for age, ethnicity, sex, body mass index (BMI), vitamin D25OH, estimated glomerular filtration rate (eGFR), diabetes status, education level, cigarette smoking, and physical activity.

Multivariate B: adjusted for age, ethnicity, sex, BMI, vitamin D25OH, eGFR, systolic blood pressure, diabetes status, education level, cigarette smoking, physical activity, and other antihypertensive medication class use (dihydropyridine-CCB: adjusted for use of thiazide, loop diuretic, non-dihydropyridine-CCB, RAAS-inhibitor, beta-blocker, and alpha-blocker; non-dihydropyridine-CCB: adjusted for use of thiazide, loop diuretic, dihydropyridine-CCB, RAAS-inhibitor, beta-blocker, and alpha-blocker).

Multivariate C: adjusted for age, ethnicity, sex, BMI, vitamin D25OH, eGFR, systolic blood pressure, diabetes status, education level, cigarette smoking, physical activity, other antihypertensive medication class use, serum calcium, serum phosphate, urinary calcium/cr, urinary phosphate/creatinine, and FGF-23.