Thiazide Treatment in Primary Hyperparathyroidism—A New Indication for an Old Medication?

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Context: There is no therapy for control of hypercalciuria in nonoperable patients with primary hyperparathyroidism (PHPT). Thiazides are used for idiopathic hypercalciuria but are avoided in PHPT to prevent exacerbating hypercalcemia. Nevertheless, several reports suggested that thiazides may be safe in patients with PHPT.

Objective: To test the safety and efficacy of thiazides in PHPT.

Design: Retrospective analysis of medical records.

Setting: Endocrine clinic at a tertiary hospital.

Patients: Fourteen male and 58 female patients with PHPT treated with thiazides.

Interventions: Data were compared for each patient before and after thiazide administration.

Main Outcome Measures: Effect of thiazide on urine and serum calcium levels.

Results: Data are given as mean ± standard deviation. Treatment with hydrochlorothiazide 12.5 to 50 mg/d led to a decrease in mean levels of urine calcium (427 ± 174 mg/d to 251 ± 114 mg/d; $P < 0.001$) and parathyroid hormone (115 ± 57 ng/L to 74 ± 36 ng/L; $P < 0.001$), with no change in serum calcium level (10.7 ± 0.4 mg/dL off treatment, 10.5 ± 1.2 mg/dL on treatment, $P = 0.4$). Findings were consistent over all doses, with no difference in the extent of reduction in urine calcium level or change in serum calcium level by thiazide dose.

Conclusion: Thiazides may be effective even at a dose of 12.5 mg/d and safe at doses of up to 50 mg/d for controlling hypercalciuria in patients with PHPT and may have an advantage in decreasing serum parathyroid hormone level. However, careful monitoring for hypercalcemia is required. **(*J Clin Endocrinol Metab* 102: 1270–1276, 2017)**

Asymptomatic primary hyperparathyroidism (PHPT) is a common disorder for which surgery is the only definitive therapy. Hypercalciuria was reintroduced as an indication for surgery at the 2013 Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism (1). However, in practice, some patients with mild to moderate hyperparathyroidism and hypercalciuria are ineligible for surgery or refuse surgical procedures. This subgroup, in addition to patients in whom prior surgery was unsuccessful, are at risk for disease-associated complications, including symptomatic hypercalcemia, osteoporosis, nephrolithiasis, and unfavorable renal

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Abbreviations: 25(OH)D, 25-hydroxyvitamin D; HCTZ, hydrochlorothiazide; PHPT, primary hyperparathyroidism; PTH, parathyroid hormone.

manifestations. Their treatment options are limited to calcimimetic agents to reduce serum calcium levels and antiresorptive medications to protect bone health (2). There is no approved targeted treatment of hypercalciuria, which exposes patients to the development of urinary calcium stones and renal dysfunction (2).

Thiazide diuretics are commonly used in clinical practice as antihypertensive agents (3). Because one of their renal effects is an increase in calcium reabsorption, they are also the treatment of choice for idiopathic hypercalciuria (4–6). Although the increase in calcium reabsorption may be associated with an increase in serum calcium, it is often mild because of the rapid suppression of parathyroid hormone (PTH) levels (7, 8). However, there are reports of severe hypercalcemia in thiazide-treated patients who were later diagnosed with PHPT, leading many physicians to obviate the use of thiazide diuretics in this patient subgroup (5, 7, 9–12). At the same time, a few small, older reports (13–15) and 1 recent study (16) suggested that thiazide diuretics may be safe in patients with PHPT.

In light of the emerging debate on the use of thiazides in patients with PHPT, we evaluated their safety and efficacy in this context. We hypothesized that thiazide treatment reduces hypercalciuria without substantial changes in serum calcium levels in patients with PHPT who are ineligible for or have failed surgery.

Methods

The study was conducted at Rabin Medical Center, a tertiary hospital in Israel, and was approved by the local institutional review board. The electronic records of 500 patients with PHPT who were followed at the endocrine outpatient clinic between 2010 and 2015 were available for review. Those who met the following criteria were included in the study: (1) surgical failure or ineligibility for surgical resection, (2) treatment with thiazide, and (3) documented biochemical data off and on thiazide treatment.

A total of 72 patients were identified. Reasons for ineligibility for surgery were suspicion of hyperplasia due to familial PHPT (3 patients), advanced age or comorbidities (9 patients), and failure to detect a parathyroid adenoma on preoperative imaging studies (16 patients). Additionally, 29 patients refused surgery and 8 had no indication for surgery. Seven patients had undergone unsuccessful parathyroidectomy in the past. Thiazide was administered in doses of 12.5 to 50 mg/d, either in the form of pills containing hydrochlorothiazide (HCTZ) or pills containing a combination of HCTZ 50 mg and amiloride 5 mg (n = 19). All patients also received vitamin D3 supplementation to a target serum level of at least 50 nmol/L 25-hydroxyvitamin D [25(OH)D].

The biochemical parameters evaluated included levels of serum and urine calcium, serum phosphorus, creatinine, PTH, and 25(OH)D. Maximum serum calcium was defined as the maximal level of serum calcium available. Mean calcium was defined as the average of 3 consecutive serum calcium tests in the presence of 25(OH)D $\geq$50 nmol/L. Urine calcium and creatinine were measured in a 24-hour collection, calcium-to-creatinine ratio was assessed, and a maximal level of calciuria was selected for the analysis. Hypercalciuria was defined as urine calcium level greater than the upper limit of the normal range in our laboratory (250 mg/d). The occurrence of symptomatic kidney stones was determined by a search of the medical follow-up reports. Findings were compared off and on HCTZ treatment of each patient.

Serum level of total 25(OH)D was measured using the Architect i2000SR Immunoassay Analyzer (Abbott Diagnostics, Irving, TX). The cross-reactivity in this assay is 105% with 25(OH)D3, 82% with 25(OH)D2, <0.3% with D2 or D3, and 12.6% with 1,25(OH_2)D3. Serum total calcium, albumin, phosphorous, and creatinine were measured using the Cobas c701 analyzer (Roche Diagnostics, Indianapolis, IN). Intact PTH was measured with the PTH Biointact (1-84) kit (normal range, 14 to 53 pg/mL; Quest Diagnostics, San Juan Capistrano, CA).

Statistical analysis

The statistical analysis was generated using SAS Software, version 9.4 (SAS System for PC; SAS Institute, Cary, NC). Continuous variables are presented as means ± standard deviations; categorical variables are given as number and percent. The *t* test was used to compare continuous variables between study groups, and the χ^2 test was used to compare categorical variables. A paired *t* test was used for comparisons of intrasubject off- and on-treatment values. Analysis of variance was used to assess the extent of change in biochemical parameters on HCTZ therapy from pretherapy levels. A P value of <0.05 was considered statistically significant.

Results

Clinical characteristics

The baseline clinical characteristics of the patients are listed in Table 1. The study cohort consisted of 58 female (81%) and 14 male patients, whose mean age was 68 ± 9 years at onset of HCTZ treatment. Of the 72 patients, 57 (79%) had hypercalciuria; in the remaining 15 patients (21%), the indication for thiazide treatment was hypertension. Mean duration of HCTZ treatment was 3.1 ± 2.3 years (range, 0.2 to 9 years). There was no difference in mean patient age or duration of HCTZ treatment by HCTZ dose (data not shown).

Biochemical parameters

The effects of HCTZ treatment on the biochemical parameters of the cohort are shown in Table 2 and Fig. 1. Effects by dose of HCTZ are listed in Tables 3 and 4.

Urine calcium

There was a marked decrease in urine calcium level (427 ± 176 mg/d off treatment to 251 ± 114 mg/d on treatment; $P < 0.001$; Table 2), which remained

Table 1. Baseline Clinical Characteristics in 72 Patients With PHPT

Characteristic	Data
Female patients, no. (%)	58 (81)
Age, mean ± SD, y	68 ± 9
Disease duration, mean ± SD, y[a]	9 ± 4
Indication for HCTZ, no. (%)	
Hypertension	15 (21)
Hypercalciuria	57 (79)
Nephrolithiasis	21 (29)
Osteoporosis	25 (35)
Fracture	5 (7)

Abbreviation: SD, standard deviation.

[a]Duration of PHPT at start of HCTZ treatment.

consistent over all HCTZ doses administered (Table 3). Results were consistent in calculations of calcium/creatinine ratio (0.403 ± 0.169 mg/d off treatment to 0.235 ± 0.112 mg/d on treatment; n = 49; $P < 0.001$). No significant difference was found in the extent of reduction in urine calcium levels between patients who received different HCTZ doses ($P = 0.9$; Table 4).

Paired values of urine calcium before and after HCTZ administration were available for 68 patients. Of the 43 patients with a baseline urine calcium level of ≥400 mg/d, 34 (79%) had a reduction to <400 mg/d on HCTZ treatment (mean, 277 ± 57 mg/24 h). The other 9 continued to have hypercalciuria while receiving HCTZ treatment, although their mean level decreased from 628 ± 144 mg/d to 465 ± 53 mg/d.

Serum calcium

HCTZ treatment had no effect on either the mean or maximal level of serum calcium (mean, 10.7 ± 0.4 mg/dL off treatment, 10.5 ± 1.2 mg/dL on treatment, $P = 0.4$; maximum, 11 ± 0.5 mg/dL off treatment, 11 ± 0.5 mg/dL on treatment, $P = 0.8$) (Table 2; Fig. 1). These findings were consistent over all doses administered (Table 3). There was no difference in the extent of change in serum calcium level between patients who received different HCTZ doses ($P = 0.2$; Table 4).

The change in urine calcium did not correlate with the change in mean serum calcium ($r = 0.06$; $P = 0.64$).

Of the 60 patients with a maximal serum calcium level <11.5 mg/dL before HCTZ treatment, 8 (13%) had increased levels of at least 11.5 mg/dL on HCTZ treatment. The mean time from starting HCTZ to reaching the maximal calcium level was 17 ± 11 months (median, 12 months; range, 5 to 36 months). The mean maximal serum calcium level in this subgroup was 11.7 ± 0.2 mg/dL compared with 10.8 ± 0.4 mg/dL in those who did not have an increase in calcium to at least 11.5 mg/dL on treatment ($P < 0.01$). Nevertheless, these 2 groups had comparable baseline biochemical parameters (Supplemental Table 1).

Eleven patients had a maximal serum calcium level of ≥11.5 mg/dL before HCTZ treatment (mean, 11.8 ± 0.2 mg/dL). After starting treatment, the maximal level decreased in 9, including 4 in whom it decreased to <11.5 mg/dL. However, in the other 2 patients, calcium levels increased from 11.8 and 11.6 mg/dL to 12.3 and 12.4 mg/dL, respectively. One was treated with 50 mg of HCTZ and showed a maximal increase in serum calcium at 6 months of drug administration. The other was treated with 25 mg of HCTZ and showed a maximal increase in calcium level at 12 months of drug administration. Both patients subsequently underwent surgery.

PTH

Mean PTH level decreased significantly, from 115 ± 57 pg/dL off treatment to 74 ± 36 pg/dL on treatment ($P < 0.001$; Table 2). These findings were consistent over all doses administered (Table 3). There was no difference in the extent of reduction in PTH level by HCTZ dose ($P = 0.74$; Table 4).

Table 2. Effect of Hydrochlorothiazide on Biochemical Parameters in Patients With PHPT

			Absolute Difference		
Parameter	Off HCTZ Tx	On HCTZ Tx	Mean	95% CI	*P* Value
Urine Ca, mg/24 h	427 ± 176	251 ± 114	177 ± 120	148 to 207	<0.001
Mean serum Ca, mg/dL	10.7 ± 0.4	10.5 ± 1.2	0.1 ± 1.2	−0.2 to 0.4	0.41
Max serum Ca, mg/dL	11.1 ± 0.5	11 ± 0.5	0.0 ± 0.6	−0.1 to 0.2	0.82
PTH, pg/dL	115 ± 57	74 ± 36	44 ± 48	31 to 56	<0.001
Vitamin 25(OH) D3, nmol/L	64 ± 12	69 ± 15	−5±14	−9 to −2	0.002
Serum P, mg/dL	2.9 ± 0.5	3.4 ± 3.3	−0.5 ± 3.3	−1.3 to 0.3	0.20
Serum Cr, mg/dL	0.7 ± 0.2	0.8 ± 0.2	−0.05 ± 0.1	−0.08 to −0.01	0.007

Data presented as mean ± standard deviation.

Abbreviations: CI, confidence interval; Cr, creatinine; Tx, therapy.

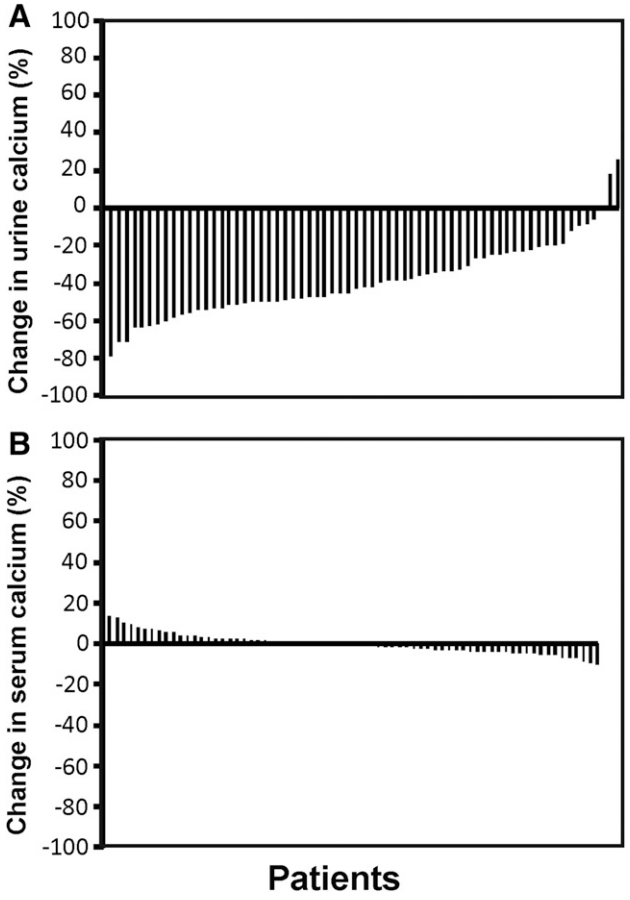

Figure 1. Effect of hydrochlorothiazide on serum and urine calcium levels in patients with PHPT. Data are presented for each patient as change (%) in (A) urine calcium levels and (B) maximal serum calcium while receiving thiazide treatment compared with baseline levels (*i.e.*, not receiving thiazide).

Other parameters

Serum phosphorus and creatinine levels were not affected by HCTZ treatment (Tables 2 and 3). Serum levels of 25(OH)D were modestly higher (69 ± 15 nmol/L) on treatment than off treatment (64 ± 12 nmol/L, $P = 0.002$; Table 2).

One-third of patients had nephrolithiasis. None had symptomatic disease during follow-up. These patients showed a similar response to the administration of HCTZ as the full cohort, with a decrease in urinary calcium from 513 ± 151 mg/d off treatment to 271 ± 105 mg/d on treatment ($P < 0.01$) and no significant change in serum calcium levels (11.0 ± 0.4 mg/dL off treatment and 11.0 ± 0.4 mg/dL on treatment; $P = 0.8$). Mean PTH level was 103 ± 41 pg/dL off HCTZ and 58 ± 25 pg/dL on HCTZ ($P < 0.01$).

Discussion

This study was prompted by the controversy surrounding the use of thiazide in patients with PHPT. We found that in patients with PHPT and hypercalciuria who are ineligible for surgery or for whom surgery was not successful, treatment with thiazide diuretics can successfully decrease urinary calcium excretion without inducing a substantial change in serum calcium level regardless of the dose used (12.5 to 50 mg/d). These results are in line with those of 3 small reports (up to 13 thiazide-treated patients with PHTP) from the 1980s (13–15) (Table 5) and a fourth, more recent study comparing 170 patients treated with thiazide before undergoing surgery for PHPT with 900 patients treated outright with surgery (16). However, paired results in individual subjects were analyzed only in the smaller studies. Therefore, using a larger cohort, we compared biochemical parameters on and off thiazide treatment in each individual patient, with a relatively long follow-up. We also compared subgroups of patients by dose of thiazide administered. Together, the findings suggest that thiazide

Table 3. Comparison of Biochemical Data for Different Doses of HCTZ

HCTZ Treatment	Urine Ca (mg/24 h)	Mean Serum Ca (mg/dL)	Max. Serum Ca (mg/dL)	PTH (pg/dL)	Serum P (mg/dL)	Serum Cr (mg/dL)
12.5 mg (n = 37)						
Off	363 ± 160	10.6 ± 0.4	11 ± 0.5	109.4 ± 49	2.9 ± 0.6	0.7 ± 0.2
On	213 ± 105	10.7 ± 0.6	11 ± 0.5	67 ± 29.0	3.8 ± 4.5	0.8 ± 0.2
P value	<0.001	0.413	0.694	<0.001	0.220	0.308
25 mg (n = 21)						
Off	435 ± 161	10.8 ± 0.4	11.3 ± 0.5	140 ± 74	2.9 ± 0.3	0.7 ± 0.2
On	260 ± 118	10.3 ± 2.1	11.1 ± 0.5	88 ± 39	3.0 ± 0.4	0.8 ± 0.2
P value	<0.001	0.274	0.314	0.002	0.635	0.033
50 mg (n = 14)						
Off	584 ± 137	10.6 ± 0.4	10.9 ± 0.5	98 ± 39	2.9 ± 0.5	0.7 ± 0.2
On	336 ± 83	10.6 ± 0.5	11.1 ± 0.6	71 ± 43	3.0 ± 0.5	0.7 ± 0.2
P value	<0.001	0.840	0.110	0.024	0.324	0.138

Data presented as mean ± standard deviation.

Abbreviations: Ca, calcium; Cr, creatinine; Max., maximum; P, phosphorus.

Table 4. Change in Biochemical Parameters Compared With Baseline Levels Before HCTZ Administration

Parameter	HCTZ Dose (mg)	% Change From Baseline, Median (Min, Max)	*P* Value
Urine Ca	12.5	−46 (−79, 25)	0.90
	25	−36 (−80, −0.1)	
	50	−41 (−63, −19)	
Serum Ca, mean	12.5	0 (−5, 18)	0.20
	25	0 (−90, 5)	
	50	0 (−7, 7)	
Serum Ca, max	12.5	−2 (−10, 15)	0.27
	25	−2 (−10, 11)	
	50	1 (−5, 14)	
PTH	12.5	−35 (−85, 22)	0.74
	25	−32 (−74, −5)	
	50	−33 (−67, 23)	

Abbreviations: Ca, calcium; Max, maximum; Min, minimum.

is probably effective already at low daily doses of 12.5 mg and safe even at high doses of 50 mg/d. To our knowledge, this study includes the largest reported group of patients with PHPT treated with a high dose of 50 mg thiazide daily. Further studies are needed to explore the mechanisms underlying our observation of positive calcium balance due to a change in calciuria without exacerbation of hypercalcemia in the context of thiazide therapy.

We detected 2 subgroups of patients with a favorable response to thiazide in whom surgery might be delayed or avoided. The first comprised patients with a baseline urinary calcium level of ≥400 mg/d, the guideline-based indication for surgery, most of whom showed a substantial decrease to below the surgical cutoff (1). The second group consisted of patients with a baseline serum calcium level of ≥11.5 mg/dL, the guideline-based indication for surgery (1), most of whom showed an absolute decrease in calcium level, even to below the surgical cutoff in some.

At the same time, we identified a minority of patients with a maximal serum calcium level that increased to >11.5 mg/dL on thiazide treatment with no upfront predictor. This finding emphasizes the need for careful monitoring of all patients with PHPT who are prescribed thiazides. Maximal hypercalcemia in these patients was reached at least 5 months after initiation of thiazide, which is considerably earlier than the ≥1 year from onset of thiazide use reported in a previous observational study of the incidence of thiazide-associated hypercalcemia in the general population (8).

Unexpectedly, PTH levels significantly decreased during treatment on all thiazide doses administered. Previous studies investigating changes in PTH levels in patients treated with thiazide reported a decrease (5, 17, 18), an increase (19), or no change (16, 20) in PTH levels. One potential confounding factor is the vitamin D status, as vitamin D deficiency *per se* results in an increase in PTH levels. Therefore, steady-state PTH levels should be evaluated after vitamin D repletion. The most recent guidelines recommend repletion of 25(OH)D in all patients with PHPT to a minimum serum level of 50 nmol/L (20 ng/dL) (1). Accordingly, a major strength of our study is the consideration of all biochemical data on and off thiazide treatment in the presence of sufficient vitamin D levels of >50 nmol/L. Although the serum levels of 25(OH)D were higher on thiazide treatment relative to baseline (69 ± 15 vs 64 ± 12 nmol/L; P = 0.002), which could theoretically have led to a decrease in PTH, the difference was too small (only 5 nmol/L) to explain the full extent of the reduction in PTH levels during treatment. In this context, it is possible that thiazide reduces parathyroid gland stimulation through renal and intestinal mechanisms (13, 21) and delays the development of PHPT (22). Further investigations are needed to determine if the reduction in PTH while receiving thiazide treatment can be confirmed prospectively and if it can affect the natural long-term course of PHPT.

Our study has inherent limitations due to its retrospective design. First, we did not have systematic information on adverse effects of thiazide, such as hyponatremia and hypokalemia, or on the development of kidney stone disease during treatment. Second, we could not obtain an accurate estimation of dietary intake of calcium throughout the study period; however, patients were advised to avoid nutritional calcium restriction and to follow the dietary reference intake for calcium as recommended by the Institute of Medicine (2). Third, only total calcium was measured; ionized calcium measurements were not available, and urine calcium/creatinine ratio was not available in all patients. Nevertheless, the homogeneous cohort followed at a single tertiary center, the assessment of paired biochemical data where each subject served as his/her own control, and the evaluation of data under conditions of vitamin D sufficiency support the validity of our results.

In summary, our data suggest that thiazide is effective in decreasing hypercalciuria, may be beneficial in decreasing serum PTH, and is apparently safe for use in most patients with PHPT. Effectiveness can be achieved already at low doses of 12.5 mg/d, and safety can be maintained at doses of up to 50 mg/d. Still, careful long-term monitoring of serum calcium levels is

Table 5. Effect of Thiazide Treatment in Patients With PHPT, by Studies in the Medical Literature

	Study				
Characteristic	**Riss *et al.* (16)**	**Farquhar *et al.* (14)**	**Klimiuk *et al.* (13)**	**Elomaa *et al.* (15)**	**Tsvetov *et al.* (Present Study)**
Patients, no.	170	13	6	3	72
Age, y	68 ± 9	54 ± 10	61 ± 13	48–53 (range)	68 ± 9
Female patients, no. (%)	139 (76)	9 (69)	4 (67)	3 (100)	58 (81)
Study design	Retrospective, between-group comparison	Retrospective, intrasubject comparison	Prospective, intrasubject comparison	Retrospective	Retrospective, intrasubject comparison
Follow-up (HCTZ treatment)	ND	1–27 mo	11 d	9–36 mo	2–108 mo
HCTZ dose, mg	≤6.25–25	0.5–50	ND	100	12.5-50
Vitamin 25(OH) D3, nmol/L	45 ± 23	ND	ND	ND	69 ± 15
Serum Ca off HCTZ tx, mg/dL	11.2 ± 0.9	10.5 ± 0.2	10.7 ± 0.1	ND	11.1 ± 0.5
Serum Ca on HCTZ tx, mg/dL	11.3 ± 0.9	10.5 ± 0.1	11.2 ± 0.2	10.4 ± 0.4	11.0 ± 0.5
Urine Ca off HCTZ, mg/24 h	322 ± 196	ND	333 ± 59	ND	427 ± 176
Urine Ca, on HCTZ tx, mg/24 h	260 ± 192[a]	ND	238 ± 50[a]	0.28–0.4 (range)[b]	251 ± 114[a]
PTH off HCTZ tx, pg/mL	186 ± 197	357 ± 526[c]	1.04 ± 0.16	ND	115 ± 57
PTH on HCTZ tx, pg/mL	185 ± 172	ND	1.05 ± 0.19[d]	0.3 ± 0.07[d]	74 ± 36[a]

Data presented as mean ± standard deviation or no. (%), unless otherwise indicated.

Abbreviations: Ca, calcium; ND, no data; tx, therapy.

[a] Statistically significant decrease from level while not receiving treatment, $P < 0.05$.

[b] Data presented in Ca/Cr (mmol/mmol). No data were obtained before thiazide was started.

[c] n-Terminal PTH; reported in picomoles per liter up to 120 pmol/L.

[d] iPTH; reported in micrograms per liter.

needed to detect cases of worsening of hypercalcemia, which cannot be predicted before the start of treatment. We believe our results may be applicable in clinical practice for the prevention of kidney stone disease in the subset of patients with PHPT who cannot or refuse to be treated surgically and for whom no targeted therapeutic regimens are available. At the same time, it is unclear whether this treatment will have affect adverse clinical consequences of chronic hypercalcemia, because there was no effect on serum calcium, and any potential clinical effects of a decrease in PTH levels remain to be explored. Further prospective studies are needed to establish the efficacy and safety of thiazides in this population, including clinical outcomes such as prevention of nephrolithiasis, potential cardiovascular benefits of thiazide (23, 24), and possible change in bone density or reduction in fracture risk (25).

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