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CASE REPORT

Thiazide increases serum calcium in anuric patients: the role of parathyroid hormone

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Abstract
Summary We evaluated the effect of hydrochlorothiazide in a sample of anuric patients on hemodialysis and found an increase in serum calcium, which occurred only in those with parathyroid hormone >300 pg/ml. This finding highlights the extra-renal effect of this diuretic and a possible role of parathyroid hormone in the mechanism.
Purpose Thiazide diuretics are commonly used in patients with chronic kidney disease to treat hypertension. Their effects on calcium and bone metabolism are not well established, once calciuria may not fully explain levels of calcium and parathyroid hormone (PTH) in this population. A previous study has suggested that thiazides require the presence of PTH as a permissive condition for its renal action. In anuric patients, however, the role of PTH, if any, in the thiazide effect is unknown.
Methods To assess thiazide extra renal effect on serum calcium and whether such an effect is reliant on PTH, hydrochlorothiazide (HCTZ) 100 mg was given orally once a day to a sample of 19 anuric patients on hemodialysis for 2 weeks. Laboratories' analyses were obtained in three phases: baseline, after diuretic use, and after a 2-week washout phase.
Results We demonstrated that serum calcium (Ca) increased in ten patients (52.6%) after HCTZ use, returning to previous levels after the washout period. Out of the 19 patients, ten presented PTH ≥ 300 pg/ml, and Ca has increased in eight of them, whereas in the other nine patients with PTH < 300 pg/ml, serum Ca has increased only in two individuals (RR risk of increase Ca 3.9; $p = 0.012$).
Conclusions HCTZ was capable of increasing serum Ca in a sample of anuric patients on hemodialysis and seems this effect is highly dependent on PTH levels. Caution is required while interpreting this result, as the small sample size might implicate in a finding caused by chance.

Keywords Diuretic · Hemodialysis · Hydrochlorothiazide · Calcium · Parathyroid hormone

Introduction

Thiazide diuretics are widely used to treat hypertension in patients with chronic kidney disease (CKD). As the prescription of diuretics increased in the last two decades so did the incidence of associated hypercalcemia. In most cases, serum calcium returns to the normal range after drug suspension, except in cases of underlying primary hyperparathyroidism. [1] The mechanism of increasing serum calcium is often explained by renal effects of thiazides: increasing urinary calcium absorption or causing metabolic alkalosis. [2, 3] However, we have recently shown that diuretics' effects on calciuria did not fully explain serum calcium levels and PTH among CKD patients. [4] Still, observational studies do not allow us to conclude the use of diuretics can directly affect PTH levels.

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Table 1 Laboratory parameters during study protocol, according to parathyroid hormone (PTH) levels

	PTH < 300 (*N* = 9)				PTH ≥ 300 (*N* = 10)			
	Baseline	HCTZ	Washout	*p*	Baseline	HCTZ	Washout	*p*
PTH (pg/ml)	186 (39, 284)	118 (44, 204)	124 (39, 248)	0.918	575 (490, 926)	683 (224, 871)	590 (482, 847)	0.717
AP (UI/l)	76 (61, 101)	77 (62, 102)	82 (61, 113)	0.809	96 (63, 169)	97 (56, 169)	115 (68, 174)	0.264
TCa (mg/dl)	8.9 (8.0, 9.6)	8.3 (7.7, 9.2)	8.7 (8.0, 10.2)	0.327	9.2 (9.1, 9.4)	9.4 (9.3, 10.1)*	9.2 (8.8, 9.7)	0.019
Mg (mg/dl)	2.4 ± 0.3	2.4 ± 0.3	2.4 ± 0.3	0.461	2.6 ± 0.5	2.5 ± 0.4	2.5 ± 0.5	0.571
P (mg/dl)	5.6 ± 1.4	5.2 ± 2.2	5.4 ± 1.6	0.759	6.0 ± 2.1	5.8 ± 2.1	5.8 ± 2.3	0.863

PTH parathyroid hormone, *AP* alkaline phosphatase, *TCa* total serum calcium, *Mg* magnesium, *P* phosphate

*$p < 0.005$ vs. baseline

A previous study has shown that the hypocalciuric effect only occurs in the presence of at least normal levels of PTH. [5]. If there is any action of thiazide in patients without renal failure, and also, the role of PTH in such situation has never been tested. Meanwhile, in CKD patients, in which calciuria is lower due to a decline of renal function [4], thiazide-induced augment in serum calcium was observed on hemodialysis patients [6], suggesting an extra renal effect on calcium metabolism. Based on this result, one can argue that thiazide effect on serum calcium is not entirely based on calcium excretion. Nevertheless, this study was conducted in the 70s and, since then, dialysis prescription and technology, clinical guidelines, and even assays for measuring PTH have substantially changed.

To assess thiazide extra renal effect on serum calcium and whether such an effect is reliant on PTH, we evaluated a sample of anuric patients on hemodialysis.

Methods

A total of 19 individuals were included, and hydrochlorothiazide (HCTZ) was given orally 100 mg once a day for 2 weeks. Blood samples were obtained in three phases: baseline, after diuretic use (HCTZ phase), and after a 2-week washout phase. Chronic glomerulonephritis and diabetes accounted for the majority of CKD etiology (84%). During the study protocol, dialysis prescription was unchanged as well as medications such as calcium salts, calcitriol, and sevelamer.

Alkaline phosphatase, phosphorus, total calcium, 25 hydroxy vitamin D, and magnesium were measured in each phase of study, according to standard techniques. Calcium was measured by an automatic colorimetric method. Parathyroid hormone (PTH) was measured by a second-generation chemiluminescence immunoassay (RR = 11–65 pg/ml; Roche immunoassay analyzer, Roche Diagnostics, Germany). This assay

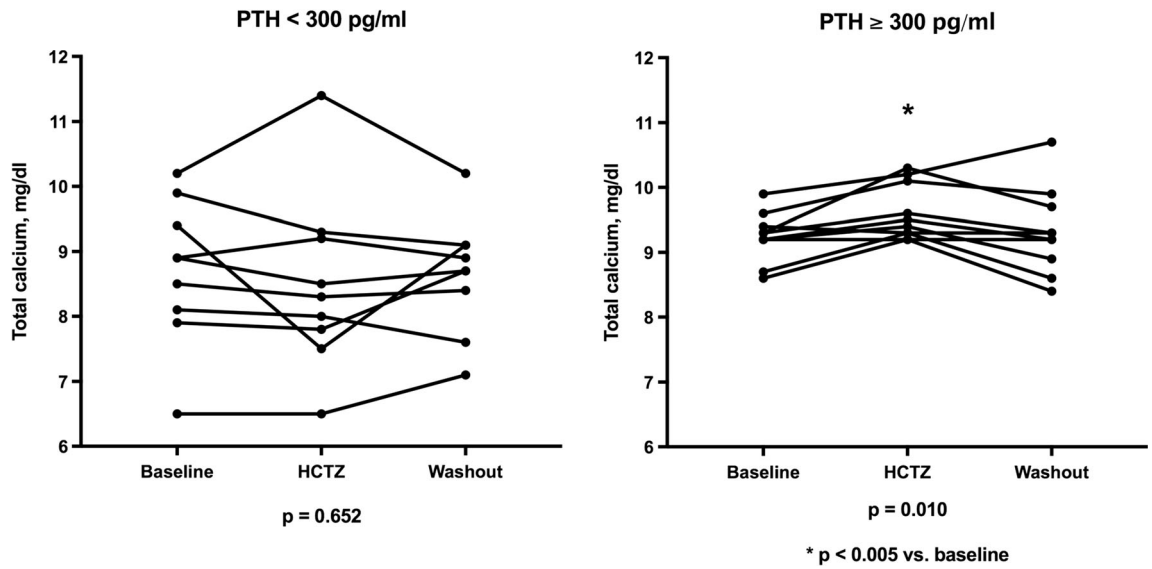

Fig. 1 Total serum calcium course during study protocol, according to parathyroid hormone (PTH) levels, <300 pg/ml (Fig. 1a) and ≥300 pg/ml (Fig. 1b)

detects both intact PTH and some inactive fragments, from 1.20 to 5000 pg/ml or 0.127 to 530 pmol/ml; CV of the method is 2.1%.

A pharmacist assessed adherence based on pill count technique.

All patients signed an informed consent. The Local Research Ethics Boards has approved this study (Cappesq #42093415.9.0000.0068).

Statistical analysis

Data are presented in mean ± SD or median (25.75) according to normality distribution, tested with D'Agostino-Pearson omnibus normality test. Mean differences in variables among baseline, HCTZ, and washout phases were assessed by repeated measures ANOVA, with Bonferroni post-test when significant, or Friedman test when appropriate. A value of $p < 0.05$ was considered significant. Analyses were performed with the use of SPSS 21.0.1 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism® software, version 6.0 (GraphPad Software, Inc., CA, USA).

Results

Patients aged 44 ± 15 years (68% were men), on hemodialysis for a median time of 4 years (2, 15). Serum calcium (Ca) increased in ten patients (52.6%) after HCTZ use when compared to the baseline, returning to previous levels after the washout period. No statistical significant changes were found in alkaline phosphatase, phosphorus, and magnesium during the study protocol, as shown in Table 1. A total of six patients had previous parathyroidectomy, in which serum calcium did not increase. In order to analyze the role of PTH in HCTZ response, we divided patients in two groups: PTH ≥ 300 and PTH < 300 pg/ml. Baseline 25 hydroxy Vitamin D levels were similar between these groups [43 (31, 56) vs. 47 (33, 59) ng/ml in patients with PTH ≥ 300 and PTH < 300 pg/ml, respectively, $p = 0.646$]. Out of the 19 patients, ten patients had PTH ≥ 300 pg/ml, and Ca increased in eight of them whereas in the other nine patients with PTH < 300 pg/ml, serum Ca has increased in two patients (RR risk of increase Ca 3.9; $p = 0.012$). As shown in Fig. 1a, when PTH is <300 pg/ml, there was no difference in serum Ca among study phases ($p = 0.652$). However, as shown in Fig. 1b, when PTH is ≥300 pg/ml, serum Ca increased at HCTZ phase and returned to baseline levels in the washout phase ($p = 0.010$).

Discussion

We have demonstrated that HCTZ was capable of increasing serum Ca in a sample of anuric patients on hemodialysis, showing the extra renal effect of this diuretic. Furthermore, it seems that the effect of HCTZ on serum Ca is highly dependent on PTH levels.

A well-known thiazide effect on calcium metabolism is increasing calcium absorption in renal tubules, and this is accepted as the primordial mechanism to cause increase in serum Ca and consequent suppression of PTH, as demonstrated in patients without CKD. [7] The CRIC study has suggested that elevations in PTH in CKD patients were related to increased calciuria by loop diuretic use. Authors also showed that thiazide could attenuate this effect by the opposite mechanism. [8] However, we have shown that calciuria in CKD patients is low and decline similarly in both groups of diuretic use (HCTZ and furosemide), as the renal function decreases. Indeed, calcium excretion was not associated with increased risk of secondary hyperparathyroidism. [4] Corroborating this mechanism, it has been demonstrated that thiazides significantly decrease calciuria, with no effect on serum calcium and PTH. [9]

A previous study has suggested that thiazides require the presence of PTH as a permissive condition for its renal action [10]. In the current study, we have found an augment in Ca after HCTZ use only in patients with high PTH > 300 pg/ml, suggesting a similar mechanism, yet of unknown meaning. Although our study design could not assess the source of calcium, whether it came from the bone or bowel, or even if its effect would last longer, we alert the scientific community on the necessity of prospective studies to elucidate thiazide extra renal effect mechanism and to better understand the impact on bone disorders. Since HCTZ is a relatively low price drug and might be used for prevention of secondary hyperparathyroidism in CKD patients, further studies are welcome.

We are aware of several limitations of the current study: the small sample size, which increases a type I error and our PTH assay detected both intact PTH and some inactive fragments; there is no control group. This limitation was partially overcome by measuring the same subject in three different situations, and also because of a washout period, we have no data on 1.25 dihydroxy vitamin D, FGF23, and bone alkaline phosphatase that would certainly help explaining our results.

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been omitted, and that any discrepancies from the study as planned have been explained.

Compliance with ethical standards

Ethical approval All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflicts of interest None.

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