

# Failure of thiazide diuretics to increase plasma calcium in mild primary hyperparathyroidism

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**Summary:** Thirteen patients with mild primary hyperparathyroidism who were taking thiazide diuretics intermittently for periods of up to 18 months were followed up for a mean of 5.3 years. No significant difference was found in either plasma total calcium corrected for albumin or whole blood ionized calcium in these patients between the periods on or off thiazides.

We conclude that thiazide diuretics are not contraindicated in such patients.

## Introduction

Hypertension is recognized as a complication of primary hyperparathyroidism. Thiazides are widely used as antihypertensive agents but these diuretics have been claimed to exacerbate hypercalcaemia in this condition.<sup>1,2</sup>

Much of the evidence for a hypercalcaemic effect of thiazides in primary hyperparathyroidism comes from short term studies. Transient increases in total plasma calcium are well documented but there is conflicting evidence of change in ultrafiltrable or ionized calcium.<sup>3–6</sup> In the absence of longer term studies of the effect of thiazides we investigated plasma calcium concentrations in patients with mild primary hyperparathyroidism who had been receiving thiazides for up to 18 months.

## Patients and methods

A retrospective study was performed on 13 patients who were being managed conservatively for mild asymptomatic primary hyperparathyroidism. The diagnosis was made by demonstrating hypercalcaemia (total calcium corrected for albumin  $> 2.60$  mmol/l, or ionized calcium  $> 1.28$  mmol/l) at the time of presentation and subsequently which was associated with inappropriately elevated plasma parathyroid hormone concentration. Nine female and four male subjects (mean age 53.9 years, range 36–71 years) were followed up for a mean of 5.3 years (range 1.5–10.7). All patients had received thiazides intermittently, and the corrected total

calcium and ionized calcium concentration were compared when they had been receiving the drug for a minimum of one month, and when they had ceased taking the drug for at least three months. These periods were chosen to avoid any transient increases in plasma calcium concentrations due to thiazide therapy.

The thiazides administered to these patients were: polythiazide 1 mg/day, cyclopentiazide 500  $\mu$ g/day, chlorthalidone 25 mg/day, bendrofluzide 2.5 or 5 mg/day and Moduretic, which contains 50 mg hydrochlorothiazide (and amiloride 5 mg), once daily.

Plasma total calcium and albumin were measured by standard methodology on a Technicon SMA 12/60 analyser. Ionized calcium was measured in anaerobically-collected whole blood using a Radiometer ICA-1 ionized calcium electrode (Radiometer A/S, Copenhagen). The corrected calcium concentration was obtained using a laboratory derived correction factor derived from the linear regression of calcium against albumin in 300 normocalcaemic subjects.

Parathyroid hormone (PTH) was measured using an N-terminal radioimmunoassay by the Supraregional Assay Service. The lower limit of detection of the assay was 40 pmol/l.

## Results

All 13 patients were shown to have primary hyperparathyroidism in that they had inappropriately elevated (9/13) or detectable (4/12) levels of PTH in the presence of hypercalcaemia (Table I). Although patient 5 did not have detectable PTH at presentation, he was later shown to have detectable PTH by an N-terminal radioimmunoassay at St.

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**Table I** Diagnostic criteria for primary hyperparathyroidism

Patient no.	Sex	Age at diagnosis (years)	Plasma total Ca corrected for albumin	Whole blood ionized Ca <sup>++</sup> (mmol/l)	N-terminal PTH (pmol/l)
1	F	42	2.74	1.49	82
2	F	54	2.58	1.34	650
3	F	36	2.82	1.44	180
4	F	50	2.73	1.36	145
5	M	60	2.95	1.43	< 40
6	F	59	2.79	1.40	175
7	M	63	2.65	1.30	110
8	M	55	2.74	N/A	370
9	F	71	2.94	1.57	230
10	F	61	2.92	1.44	> 2000
11	F	45	2.99	1.49	500
12	M	60	2.66	1.39	140
13	F	45	2.61	1.38	115

Laboratory reference ranges: total calcium 2.20–2.60 mmol/l; ionized calcium 1.20–1.28 mmol/l; N-terminal PTH up to 120 pmol/l.

George's Hospital when this assay became available.

There were 23 episodes in which a patient had a period on thiazides followed by a period off thiazides or *vice versa* (Table II). The average duration of thiazide therapy was 6.5 months (Range 1–27 months). There was no significant difference in corrected total calcium when comparing patients on or off thiazides. In 14 of these paired episodes ionized calcium measurements were made, and similarly showed no significant difference.

## Discussion

The results of this study do not provide evidence that patients with mild primary hyperparathyroidism are at risk from exacerbating pre-existing hypercalcaemia when taking thiazide diuretics.

The effect of thiazide diuretics upon calcium metabolism has been widely studied. Their main action is to reduce the urinary excretion of calcium,

predominantly by increasing renal tubular reabsorption. Thiazides have been reported to cause hypercalcaemia in chronic renal failure, when urinary calcium excretion is already minimal, suggesting that bone resorption may play a role.<sup>7</sup> In patients with normal calcium homeostasis, it is very uncommon for thiazides to induce hypercalcaemia,<sup>8</sup> as increased plasma calcium concentration suppresses parathyroid hormone secretion. However, patients with primary hyperparathyroidism show no decrease in parathyroid hormone excretion when given thiazides.<sup>9</sup>

Normal subjects who were studied for up to 2 weeks after a 4-week course of the diuretic, had significantly increased total and ionized calcium values while immunoreactive parathyroid hormone remained normal.<sup>8</sup> By contrast, increases in plasma calcium (corrected for protein) were not found in healthy subjects after 4 days on thiazides, although significant increases were observed in patients with hyperparathyroidism.<sup>3</sup> Jorgensen *et al.*, however, were unable to demonstrate any change in ultrafiltrable or ionized calcium after 5

**Table II** Effect of thiazide diuretics on corrected total and ionized calcium in mild primary hyperparathyroidism

	Corrected calcium		Ionized calcium	
	Off thiazides	On thiazides	Off thiazides	On thiazides
No. of episodes	23	23	14	14
Mean (mmol/l)	2.615	2.624	1.436	1.428
Range* (mmol/l)	2.31–3.16	2.34–3.06	1.29–1.68	1.27–1.57
SEM (mmol/l)	0.037	0.036	0.031	0.025
Paired t test	NS		NS	

\*Min-max values; NS = not significant.

days of hydrochlorothiazide in 10 hyperparathyroid patients.<sup>4</sup>

We were unable to find reports of the effect of long term thiazide administration in primary hyperparathyroidism. Klimiuk *et al.* reported on 6 hypercalcaemic patients receiving thiazides who were subsequently found to have primary hyperparathyroidism. Withdrawal of the diuretic for 6 days led to a small but significant fall in total serum

calcium.<sup>9</sup> The significance of this finding is limited by the brief duration of the study.

It is concluded that despite assertions to the contrary<sup>1,2</sup> the prolonged use of thiazides in mild primary hyperparathyroidism does not lead to a significant increase in plasma calcium or whole blood ionized calcium concentration. It is our view that these drugs need not necessarily be withheld in this group of patients.

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