Incidence of hypercalcemia and thiazide associated hypercalcemia on an OPD basis in a Tertiary referral hospital

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ABSTRACT

Background: Hypercalcemia is most of the times diagnosed on routine biochemical evaluation, and concomitant use of thiazide diuretics is common since this group of antihypertensives is frequently prescribed worldwide.

Objective: To determine the incidence of hypercalcemia as well as thiazide-induced hypercalcemia on OPD basis

Material and Methods: In a prospective hospital-based descriptive study, patients for routine evaluation, attending outpatient clinics were included.

Results: A total of 373 patients participated in the study, out of which 101 (27.1%) were hypertensive. 30 of the 101 hypertensive patients were on thiazides. Hypercalcemia was present in total of 7 (1.9%) patients, primary hyperparathyroidism was seen in 4 patients, out of which 2 patients were on thiazides. 6.7% (2/30) of the patients on thiazides were having hypercalcemia as compared to 1.5% (5/343) patients, not on thiazides ($p=0.044$).

Conclusion: About every 50 patients evaluated, one patient has hypercalcemia with frequency of hypercalcemia being significantly higher among subjects receiving thiazides than those not receiving thiazide drugs.

Key Words: Hypercalcemia, thiazides, primary hyperparathyroidism

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INTRODUCTION

There has been a continuing interest in the incidence of hypercalcemia and its underlying causes. This interest stems both from the frequency and ease with which calcium estimations are done on routine blood analysis and the implication that hypercalcemia may act as a marker of an underlying disease. Of many causes of symptomatic and asymptomatic hypercalcemia, primary hyperparathyroidism (PHPT) is an excellent example of a disease where repeated attempts have been made to estimate incidence and frequency. These estimates have, however, varied widely, depending upon the methodology used. Thiazides are the first-line treatment in essential

hypertension and reduce mortality and cardiovascular events¹. Hydrochlorothiazide is the most commonly prescribed antihypertensive medication worldwide. In 2008, there were nearly 135 million prescriptions in the United States when combination products with hydrochlorothiazide, which comprise approximately two-thirds of total prescriptions, were included².

Hypercalcemia associated with thiazide use is a well-known

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clinical entity. Thiazides exert their antihypertensive effect through an increase in sodium excretion by blocking the thiazide-sensitive NaCl transporter in the distal convoluted tubule, which is closely linked to calcium transport. Increased renal tubular reabsorption of calcium occurs, resulting in reduced urine calcium excretion, is the most likely cause³. Serum calcium concentrations are increased independently of PTH levels⁴. The epidemiology of thiazide-associated hypercalcemia is poorly known. In a prospective health screening study by Christensson et al, the prevalence of hypercalcemia in individuals (20 to 63 year old) on thiazide diuretics was reported to be 1.9%⁵. The prevalence was three times higher than observed in same-aged subjects in the general population, not on thiazides (0.6% prevalence). Most of the individuals were older hypertensive women (90%) on treatment for 1-15 years. Withdrawal of thiazides resulted in persistent hypercalcemia in 75% after 1 year of follow-up. Subsequently, 70% of these subjects underwent parathyroidectomy for primary hyperparathyroidism (PHPT).

A study in Sweden carried by Heedman PA et al evaluating hypercalcemia after the introduction of automated chemistry panels in a single county hospital estimated that the prevalence of hypercalcemia in thiazide-treated adults was 0.4%, again approximately two to three times higher than was observed in the general population, not on the thiazides⁶. The hypercalcemia associated with thiazides was mild and predominantly in females (80%). Wermers et al did a population-based descriptive study, in Olmsted County, Minnesota, where medical care is essentially self-contained within this community (approximately 124,000 residents) and where most endocrinological care is provided by the Mayo Clinic, which has maintained a common medical record for over 100 years, found that between 1992 and 2001, annual incidence of thiazide-associated hypercalcemia was 7.7 per 100,000, with 90% patients being elderly females. Approximately two-thirds of the patients with thiazide-associated hypercalcemia have underlying concomitant primary hyperparathyroidism⁷. The incidence increased to 12.2 per 100,000, in the same population, in 2010⁸. We therefore undertook this study, to determine, by a prospective screen, the incidence of hypercalcemia, thiazide induced hypercalcemia and the

frequency distribution of its causes at our Institution.

MATERIALS AND METHODS

A prospective screening of all patients over a period of one year, (December 2017 to December 2018), attending outpatient clinics of a tertiary care hospital in North-India, in whom serum calcium had been asked in their blood work up and were willing to participate in the study were recruited. A total of 373 patients participated in the study after taking proper consent. A preformed proforma was used to enter the details of all patients, including demography, comorbidities, and drug history. Hypercalcemia was defined as albumin-adjusted total serum calcium more than 10.8 mg/dl (normal reference range =8.8-10.8 mg/dl). All the patients with hypercalcemia were called telephonically, for confirmation and evaluation of hypercalcemia. After detailed history and examination, serum calcium was repeated in hypercalcemic patients along with creatinine, 25 Hydroxy Vitamin D levels, and parathyroid hormone(PTH) levels among other investigations. Etiology of hypercalcemia was evaluated under two groups: i) PTH dependent v/s independent etiology; ii) Thiazide user v/s non-user. Primary hyperparathyroidism was diagnosed as sustained hypercalcemia with PTH level > 20 pg/ml. Patients were accepted as having thiazide-associated hypercalcemia if they met the following criteria: sustained hypercalcemia (serum calcium ≥ 10.8 mg/dL) documented on two or more measurements with concomitant thiazide diuretic use for which no other cause (eg, pathologically or biochemically proven PHPT before initiation of thiazides, malignancy, family history of familial benign hypocalciuric hypercalcemia, renal disease, or lithium therapy) was identified. Vitamin D related hypercalcemia was defined as sustained hypercalcemia with 25 Hydroxy Vitamin D levels >100 ng/ml.

Statistical Analysis: Data were managed in Microsoft Excel 2016 and exported to Statistical Package for the Social Science® (SPSS) for Mac version 25.0 software (SPSS Inc., Illinois, USA) for further analysis. Numbers and percentages were used to present categorical data. Mean ($\pm$ standard deviation, [SD]) was used for normally distributed continuous data. The significance of differences between the two groups was examined by Student's t-test or Mann-Whitney U test (in the case the distribution of the variable in question was not normal). The χ^2 test of independence was

used for qualitative variables (respectively using Yates' correction and Fisher's exact test as appropriate). In order to establish the strength and direction of the association between variables the Pearson and/or Spearman correlation tests were used. In all the calculations the level of significance was set at $p=0.05$.

RESULTS

A total of 373 patients (216 females) participated in the study. The mean age of patients was 42.07 ± 13.97 years, and mean age of males was higher than that of females (43.6 v/s 40.9 years). Most patients were in the age group of 40-49 years (table 1). The mean calcium level in males was 9.55 ± 0.70 mg/dl and that in females was 9.41 ± 0.59 mg/dl ($p=0.15$). 225 (60%) were having a comorbid illness. Hypertension was present in 101 (27.1%) patients, out of whom 30 were on thiazides. Second most common comorbidity was hypothyroidism present in 38 patients (10.2%) followed by type 2 diabetes which was seen in 26 patients, CKD in 7, malignancy in 6 and 3 patients were post renal transplant (Table 2). Mean serum calcium of the cohort was 9.5 mg/dl. Patients on thiazides had higher serum calcium values (9.8 ± 0.84 mg/dl) than the rest of the cohort (9.47 ± 0.65 mg/dl) with a p -value of 0.01 (table 3). Once calcium values were divided into quartiles, 12 % of patients in the fourth quartile had a history of thiazide intake as compared to 8%, 6% and 6% in third, second and first quartile respectively.

Table 1 : Age and gender distribution of the patients.

Age Group (years)	Male (n=157)	Female (n=216)	Total (n=373)
<30	21 (13.3%)	47 (22.2%)	69 (18.5%)
30-60	115 (63.2%)	142 (65.7%)	257 (68.9%)
>60	21 (13.4%)	26 (12%)	47 (12.6%)

Table 2 : Associated comorbidities of the Study population (n=373)

Comorbidity	N	Percent
Any co-morbidity	148	(40%)
Hypertension	101	(27.1)
Hypothyroidism	38	(10.2)
Type 2 Diabetes	26	(7.0)
CKD	7	(1.9)
Malignancy	6	(1.6)
Post-Transplant	3	(0.8)
No major comorbidity	225	(60%)

Table 3: Serum calcium levels in patients taking thiazides vs rest of the cohort

Thiazide intake	N	Serum calcium (mg/dl)	
		Mean $\pm$ SD	95% CI for Mean
No	343	9.47 ± 0.65	9.40–9.54
Yes	30	9.80 ± 0.84	9.49–10.11
Total	373	9.50 ± 0.67	9.43–9.57

$P = 0.01$

A total of 7 patients had hypercalcemia of whom 2 had a history of thiazide intake. One of the patients had diabetes mellitus. So among thiazide users, 6.7% (2/30) were hypercalcemic, compared to 1.5 % (5/343) in the rest of the cohort ($p=0.004$) (Fig. 1). Among 5 hypercalcaemic patients seen, 4 were eventually diagnosed to have primary hyperparathyroidism among which two had concomitant thiazide intake, one was found to have vitamin D intoxication, and 2 had hypercalcemia of unknown aetiology.

DISCUSSION

The reported incidence of hypercalcemia varies widely. Many biochemistry laboratories in recent years have added serum calcium profile to their routine service. This approach simplifies work within the laboratory, but the clinical usefulness of the approach has been debated^{9,10}. Inclusion of a plasma calcium determination in the profile leads both to an increase in the number of patients identified as hypercalcemic and in the diagnosis of hyperparathyroidism^{6,11,12}.

Over a period of one year, hypercalcemia was observed in 1.9% of patients undergoing a routine investigatory biochemical profile with serum calcium as one of the parameters. Our incidence of 1.9% is higher than the reported range of 0.2-1.36% reported from hospitals with outpatient clinic analysis (13,14). This might be due to the reason that we included only those patients where serum calcium was a part of the evaluation. Christenson who did the screening of apparently healthy adults found the incidence of hypercalcemia of 0.6% (after excluding transient hypercalcemia)(15). PHPT was the most common cause of hypercalcemia, seen in 4 out of 7 patients (57%). One patient had Vitamin D related hypercalcemia after a history of 10 injections of vitamin D (6 lakh IU in each vial).

101 patients (27.1%) were hypertensive, out of which 30 were on thiazides (all were on hydrochlorothiazide). Thiazides are the most commonly prescribed antihypertensive medication worldwide. One potential explanation for this trend could be the increased use of thiazides since the ALLHAT Trial¹⁶. Also, thiazides are inexpensive and effective antihypertensive agents with proven cardiovascular benefit. Two patients on thiazides had hypercalcemia, and both the patients were on this drug for more than 5 years. Both the patients, on further evaluation, proved to have PHPT. So 6.6% of patients on thiazides were having thiazide related hypercalcemia as compared to 1.5% in the rest of the cohort (4 times). There are many case reports of thiazide-induced hypercalcemia and a few case series of thiazide related hypercalcemia. Christenson found that 1.9% of individuals on thiazides were having hypercalcemia as compared to 0.6% of the whole cohort, so three times more common⁵. Another study from Sweden evaluating hypercalcemia after the introduction of automated chemistry panels in a single county hospital estimated that the prevalence of hypercalcemia in thiazide-treated adults was 0.4%, again approximately two to three times higher than was observed in the general population¹⁷.

Since the early 1970s, only two studies have evaluated the epidemiology of thiazide-associated hypercalcemia. In one study, from 1991 to 2001, the overall age and sex-adjusted annual incidence of thiazide-associated hypercalcemia was 7.7 per 100 000 among residents of Olmsted County, Minnesota⁷. Another study by Griebeler ML et al, the continuation of the previous one, reported a decade later found the incidence of thiazide-associated hypercalcemia to be 12.2 per 100000⁸. Once calcium values were divided into quartiles, 12 % of patients in the fourth quartile had a history of thiazide intake as compared to 8%, 6% and 6% in third, second and first quartile respectively.

Both the patients of thiazide-induced hypercalcemia were found to have PHPT. Wermer also found that after excluding readily identifiable causes of hypercalcemia, approximately two-thirds of the patients with thiazide-associated hypercalcemia have underlying primary hyperparathyroidism⁷. In another study, as many as 71% of subjects with thiazide-associated hypercalcemia have underlying PHPT based on the persistence of

hypercalcemia in those who discontinue the medication⁸. Thiazide related hypercalcemia settled in 20-30 % of patients in whom the drug was stopped. There is an increasing trend in the thiazide-induced hypercalcemia, and the trend is paralleling the increase in the incidence of PHPT, which is nowadays diagnosed incidentally. 80-90% of these patients are reported to be elderly females. Hypertension and PHPT are both being the diseases of the elderly, and thiazides are the most common antihypertensives used. Some authors strongly believe that thiazides unmask the hypercalcemia of PHPT, on their introduction.

Various mechanisms have been proposed by which thiazides are associated with an increase in serum calcium level. A reduction in urine calcium excretion is the most likely explanation, but a metabolic alkalosis associated with diuretic use could also cause an elevation in total serum calcium through a pH-dependent increase in protein-bound calcium¹⁸. Although plasma $1,25(\text{OH})_2$ Vitamin D levels are unchanged, increased intestinal calcium absorption in response to thiazide treatment has been noted and could also contribute to an increase in serum calcium^{19,20}. A final factor that may lead to the development of hypercalcemia is hemoconcentration associated with diuresis²¹.

The appropriate clinical management of patients with thiazide-associated hypercalcemia is poorly delineated. After confirming sustained hypercalcemia, a serum parathyroid hormone determination is useful in narrowing the diagnostic considerations. Although thiazides are often discontinued to determine if they are the cause of the hypercalcemia, the hypercalcemia has been described as mild, non-progressive, and often consists of a temporary elevation shortly after the onset of therapy⁵. In patients without an easily identifiable cause of hypercalcemia on thiazides and an unsuppressed parathyroid hormone level, a reasonable strategy may be to follow guidelines for asymptomatic primary hyperparathyroidism after stopping thiazides²². Whereas aggravation of hypercalcemia is a concern if thiazides are continued, it appears that thiazides do not exacerbate hypercalcemia in patients who develop mild primary hyperparathyroidism²³. Limitations of the study include a limited number of patients and hospital study rather than a community-based.

In conclusion, after every 50 patients evaluated on routine OPD basis, one patient proves to have hypercalcemia. Among hypertensive patients on thiazides, 6.7% of patients had hypercalcemia with PHPT being the underlying cause.

DECLARATIONS

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