BRITISH JOURNAL OF HOSPITAL MEDICINE

REVIEW

Thiazide diuretics and primary hyperparathyroidism

Simon Mifsud[1]

Gabriella Montanaro[2]

Sarah Craus[1]

Emma L Mifsud[2]

Mark Gruppetta[1]

Author details can be found at the end of this article

Correspondence to:
Simon Mifsud;
simon.a.mifsud@gov.mt

Abstract

Thiazide diuretics exert a natriuretic and diuretic effect by inhibiting sodium reabsorption in the distal convoluted tubule. Furthermore, thiazide diuretics affect renal calcium handling by increasing calcium reabsorption, leading to hypocalciuria. The effect that thiazide diuretics exert on parathyroid hormone secretion is controversial. Some studies found parathyroid hormone levels were suppressed with the use of thiazide diuretics, while others found that thiazides were associated with initial parathyroid hormone suppression followed by raised parathyroid hormone levels. This makes the relationship between thiazide diuretics and primary hyperparathyroidism interesting. If a patient is taking thiazide diuretics, this may make it harder to establish the aetiology of hypercalcaemia and may unmask normocalcaemic or mild primary hyperparathyroidism. Thiazide diuretics may have a beneficial role in the diagnosis of patients with concomitant hyperparathyroidism and hypercalciuria by distinguishing secondary hyperparathyroidism caused by hypercalciuria from normocalcaemic primary hyperparathyroidism. In addition, thiazide diuretics may have a role in managing patients with primary hyperparathyroidism who have an indication for parathyroidectomy in view of significant hypercalciuria, but are unfit for surgery.

Key words: Hypercalcaemia; Hyperparathyroidism; Thiazide diuretics

Submitted: 21 June 2023; accepted following double-blind peer review: 11 September 2023

Introduction

Thiazide diuretics are a class of drugs that block the sodium–chloride channel in the proximal segment of the distal convoluted tubule of the nephron, causing natriuresis and diuresis (Akbari and Khorasani-Zadeh, 2023). In addition, they affect renal calcium handling by increasing calcium reabsorption, leading to hypocalciuria, although the mechanism by which they do this is unclear. Thiazide-induced hypocalciuria can be secondary to passive paracellular calcium reabsorption in the proximal convoluted tubule following the reduction of the extracellular volume (Nijenhuis et al, 2005; Bergsland et al, 2013). Rodent studies revealed another possible mechanism for thiazide-induced hypocalciuria, through calbindin expression and the upregulation of calcium channels such as transient receptor potential cation channel subfamily V member 5 in the distal convoluted tubule (Nijenhuis et al, 2005).

Given the latter mechanisms, the effect that thiazide diuretics exert on parathyroid hormone secretion is controversial. Thiazides can interfere with the diagnostic process of primary hyperparathyroidism and may worsen hypercalcaemia in patients with primary hyperparathyroidism, but they may also have beneficial diagnostic and therapeutic roles in these patients.

This review is based on guidelines and literature found via MEDLINE (PubMed) from 1973 to 2023. The keywords used were: ‘thiazide diuretics, ‘hyperparathyroidism’ and ‘parathyroid hormone’. Additional relevant publications were manually obtained from other cited papers in retrieved articles. This review focuses on the physiology of parathyroid hormone secretion in patients taking thiazide diuretics, as well as the potential beneficial and interfering roles that these medications may play in patients with hyperparathyroidism.

Physiology of calcium homeostasis

Serum calcium levels in humans are tightly controlled by parathyroid hormone, 1,25-dihydroxyvitamin D and calcitonin (Turner et al, 2018). When serum calcium levels drop, the calcium-sensing receptor on the chief cells of the parathyroid gland stimulate

How to cite this article:
Mifsud S, Montanaro G, Craus S, Mifsud EL, Gruppetta M. Thiazide diuretics and primary hyperparathyroidism. Br J Hosp Med. 2023. https://doi.org/10.12968/hmed.2023.0228

synthesis and release of parathyroid hormone into the circulation. Parathyroid hormone increases serum calcium concentration through increased renal calcium reabsorption and decreased phosphate reabsorption. In the kidney, parathyroid hormone also promotes the 1-alpha-hydroxylation of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D. The latter acts on the gastrointestinal tract promoting calcium absorption. Furthermore, parathyroid hormone stimulates osteoclast resorption which releases calcium and phosphate into the systemic circulation (Turner et al, 2018).

Once the calcium concentration rises, calcium-sensing receptors on the parathyroid gland chief cells inhibit further release of parathyroid hormone through a negative feedback loop and the thyroid parafollicular cells secrete calcitonin. Through its effect on osteoclasts, calcitonin inhibits bone resorption and reduces the release of calcium from bone. Additionally, calcitonin inhibits renal reabsorption of phosphate and induces mild natriuresis and calciuresis, further contributing to its hypocalcaemic effect (Turner et al, 2018; Shaker and Deftos, 2023).

Primary hyperparathyroidism

Primary hyperparathyroidism is biochemically defined as hypercalcaemia with an elevated or inappropriately normal level of parathyroid hormone on two occasions (Bilezikian et al, 2022). In primary hyperparathyroidism (one of the most common causes of hypercalcaemia), there is excessive secretion of parathyroid hormone from clonally dysregulated proliferation of parathyroid tissue. Another pathophysiological hallmark is reduced expression of the cell surface calcium-sensing receptor, thus increasing the set-point for calcium-induced inhibition of parathyroid hormone, establishing a higher, generally stable serum calcium level (Bilezikian et al, 2022). Primary hyperparathyroidism is more common in women and people of Black ethnicity, and its incidence increases with age (Yeh et al, 2013; Walker and Bilezikian, 2021).

The commonest cause of sporadic primary hyperparathyroidism is a solitary parathyroid adenoma, occurring in 85% of patients. The remaining 15% of cases of primary hyperparathyroidism are secondary to multiple parathyroid adenomas, multi-glandular hyperplasia or parathyroid carcinomas (<1%) (Walker and Bilezikian, 2021; Bilezikian et al, 2022).

Primary hyperparathyroidism is associated with accelerated bone resorption, enhanced renal tubular calcium reabsorption and intestinal calcium absorption. Hypophosphataemia usually occurs as a result of reduced reabsorption of renal phosphate (Walker and Bilezikian, 2021; Bilezikian et al, 2022).

These pathophysiological effects can have significant clinical consequences. Increased bone resorption results in bone loss and osteoporosis, preferentially at cortical sites. The overstimulation of renal 1-alpha-hydroxylation leads to increased 1,25-dihydroxyvitamin D production, which facilitates intestinal calcium absorption, contributing to hypercalcaemia and eventually hypercalciuria. In turn, hypercalciuria predisposes patients to nephrocalcinosis and nephrolithiasis (Turner et al, 2018; Bilezikian et al, 2022). Furthermore, rapidly rising serum calcium levels and severe hypercalcaemia may lead to inhibition of neuromuscular and myocardial depolarisation. The latter predisposes such patients to arrhythmias such as supraventricular arrhythmias and rarely complete heart block (Ramakumar et al, 2021; Sadiq et al, 2023). Other cardiovascular effects include short QT intervals, widened QRS complexes and prolonged PR intervals (Sadiq et al, 2023).

Effects of thiazide diuretics on levels of calcium and parathyroid hormone

The fifth international workshop for the evaluation and management of primary hyperparathyroidism's summary statement and guidelines stated that thiazides are associated with hypercalcaemia and elevated levels of parathyroid hormone. However, there is controversy in the literature about the effect that thiazides have on parathyroid hormone levels. Some studies suggest that they are increased (Nowack et al, 1992; Rejnmark et al, 2001) and others show a reduction in parathyroid hormone (Nowack et al, 1992; Zaheer

et al, 2016; Tsvetov et al, 2017). There is some evidence that levels of parathyroid hormone are not altered significantly by thiazides (Giles et al, 1992; Rejnmark et al, 2001).

Coe et al (1973) reported lowering of parathyroid hormone levels in subjects with secondary hyperparathyroidism brought on by idiopathic hypercalciuria following thiazide administration. The latter was also highlighted in a small study by Sakhaee et al (1985) whereby a drop in parathyroid hormone levels with thiazide use was seen in eight subjects with postmenopausal osteoporosis as a result of renal hypercalciuria with secondary hyperparathyroidism. Similar findings were observed in a clinical trial involving 18 children with idiopathic hypercalciuria with secondary hyperparathyroidism (Reusz et al, 1998).

Interestingly, a small study involving healthy subjects with no renal disease revealed that, while acute administration of hydrochlorothiazide led to initial suppression of parathyroid hormone, sub-acutely metabolic alkalosis, lower serum ionised calcium concentration in conjunction with raised parathyroid hormone levels and reduced 1,25-dihydroxyvitamin D concentrations were observed (Nowack et al, 1992).

Another study revealed that 7 days post-thiazide administration, parathyroid hormone levels were increased in postmenopausal women compared with a placebo group (Rejnmark et al, 2001). This study also reported that the increased parathyroid hormone levels may be secondary to the thiazide-induced hypokalaemic metabolic alkalosis. The pH-dependent equilibrium shifts may lead to a reduction in serum ionised calcium (as a result of enhanced calcium–albumin binding), promoting parathyroid hormone secretion (Rejnmark et al, 2001). This is similar to the findings of Nowack et al (1992), with one notable difference. Rejnmark et al (2001) found significantly elevated plasma levels of 1,25-dihydroxyvitamin D as a result of parathyroid hormone-induced enhanced renal 1-alpha-hydroxylase activity, whereas Nowack et al (1992) reported reduced concentrations.

The combined effects of hypocalciuria and increased intestinal absorption of calcium (driven by increased 1,25-dihydroxyvitamin D) lead to a positive calcium balance in patients treated with thiazides. Unlike previous studies that reported decreased parathyroid hormone levels with thiazide treatment, Rejnmark et al's (2001) study did not involve patients with baseline hypercalciuria and elevated parathyroid hormone levels.

One major limitation was the short duration of observation, ie 7 days, by Rejnmark et al (2001). A letter to the editor by Yacobi-Bach et al (2015) discussed Rejnmark et al's (2001) work, stating that thiazide diuretics are associated with an initial increase in parathyroid hormone levels which eventually regress to near baseline at the end of the study period. Yacobi-Bach et al (2015) suggested that thiazides should be removed from the list of drugs that increase serum levels of parathyroid hormone.

A study by Zaheer et al (2016) supports Yacobi-Bach et al's (2015) letter. They found that hypertensive patients who were taking thiazide diuretics for at least 2 weeks had significantly lower parathyroid hormone levels than patients on loop diuretics and calcium-channel blockers. Moreover, the participants taking thiazide diuretics had higher serum calcium levels, and a lower urinary calcium/creatinine ratio compared to the rest of the study population.

While both Rejnmark et al (2001) and Zaheer et al (2016) found that patients on thiazide diuretics had decreased urinary calcium levels and a positive calcium balance, there were conflicting results with regards to parathyroid hormone levels. Hence, the exact relationship between thiazide diuretic use and parathyroid hormone secretion remains elusive.

Diagnosing primary hyperparathyroidism: do thiazide diuretics help or hinder?

The differential diagnoses of hypercalcaemia in the context of elevated or inappropriately normal parathyroid hormone levels are primary hyperparathyroidism, familial hypocalciuric hypercalcaemia, thiazide diuretic use, lithium-associated hyperparathyroidism and ectopic parathyroid hormone secretion.

Familial hypocalciuric hypercalcaemia is an autosomal dominant condition caused by mutations in the calcium-sensing receptor gene. Patients with the heterozygous mutation usually have normal or mildly elevated parathyroid hormone levels and exhibit mild hypercalcaemia, hypocalciuria and hypophosphataemia. These patients do not develop

complications and hence no active treatment or monitoring is required. However, patients with the homozygous mutation can present with severe hypercalcaemia and its complications (Afzal and Kathuria, 2023).

Differentiating familial hypocalciuric hypercalcaemia from primary hyperparathyroidism is challenging as these conditions have considerable overlap in their clinical features. The consensus biochemical investigation to differentiate between primary hyperparathyroidism and familial hypocalciuric hypercalcaemia is the calcium:creatinine clearance ratio in conjunction with genetic analysis (Shinall et al, 2013).

Since thiazides are associated with hypocalciuria and low calcium:creatinine clearance ratios, they can interfere with the diagnostic process of hypercalcaemia (Riss et al, 2016). Serum and urinary calcium and creatinine measurements should ideally be repeated at least 1 week after withdrawing treatment (Bollerslev et al, 2022).

Furthermore, one of the clinical phenotypes of primary hyperparathyroidism is normocalcaemic primary hyperparathyroidism, characterised by the presence of elevated parathyroid hormone levels in the setting of normal calcium levels. Thus, given this definition, normocalcaemic primary hyperparathyroidism is a diagnosis of exclusion after plausible causes of secondary hyperparathyroidism have been ruled out. Secondary hyperparathyroidism is increased levels of parathyroid hormone secretion triggered by hypocalcaemia, hyperphosphataemia or decreased concentrations of active vitamin D (Muppidi et al, 2023). The most common causes of secondary hyperparathyroidism are listed in Table 1 (Zavatta and Clarke, 2020; Bollerslev et al, 2022).

Differentiating between normocalcaemic primary hyperparathyroidism and secondary hyperparathyroidism in patients with hypercalciuria secondary to renal losses is challenging. Thiazide diuretics reduce urinary calcium losses by increasing reabsorption of calcium. This increases serum calcium levels and inhibits further secretion of parathyroid hormone in patients with secondary hyperparathyroidism caused by hypercalciuria. Thiazide diuretics may help in differentiating between normocalcaemic primary hyperparathyroidism and secondary hyperparathyroidism caused by hypercalciuria, since normalisation of serum parathyroid hormone levels with short-term thiazide therapy indicates the latter (Eisner et al, 2009; Bollerslev et al, 2022). Eisner et al (2009) proposed using a thiazide challenge test in patients with elevated parathyroid hormone levels and hypercalciuria. This involves administration of hydrochlorothiazide 25 mg twice a day for 14 days with serum parathyroid hormone measurement pre-thiazide initiation and on day 14.

A therapeutic role for thiazide diuretics?

Kidney stones

Primary hyperparathyroidism is associated with variable renal calcium handling. Hypercalciuria is defined as urine calcium excretion >4 mg/kg of body weight/24 hours

Table 1. Common causes of secondary hyperparathyroidism

Hypovitaminosis D	
Insufficient calcium intake	
Malabsorption and inflammatory bowel disease	
Chronic kidney disease	
Medications	■ Diuretics ■ Lithium ■ Bisphosphonates ■ Denosumab ■ Proton pump inhibitors ■ Sodium-glucose co-transporter 2 inhibitors
Idiopathic hypercalciuria	
Phosphate metabolism disorders	

in the presence of preserved kidney function and is observed in 18–40% of patients with primary hyperparathyroidism (Corbetta et al, 2005). Hypercalciuria is a major risk factor for development of renal calculi, and hyperoxaluria and hyperphosphaturia also contribute to renal stone formation in patients with primary hyperparathyroidism (Verdelli and Corbetta, 2017).

As per the summary statement and guidelines from the fifth international workshop for the evaluation and management of primary hyperparathyroidism, one indication for parathyroidectomy in primary hyperparathyroidism is the presence of nephrocalcinosis or nephrolithiasis or hypercalciuria (>250 mg/24 hours and >300 mg/24 hours in women and men respectively) (Bilezikian et al, 2022). In patients with primary hyperparathyroidism, parathyroidectomy lowers the risk of recurrence of kidney stones (Verdelli and Corbetta, 2017). However, there is no recommended treatment that directly addresses hypercalciuria for patients who are unfit for surgery, fail surgery or decline surgical intervention. The non-surgical approaches include bisphosphonates, which have inconsistent effects on urine calcium excretion, and cinacalcet, which has no effect on 24-hour urinary calcium excretion (Prochaska et al, 2017; Verdelli and Corbetta, 2017; Bilezikian et al, 2022).

Thiazide diuretics increase renal calcium reabsorption, leading to a significant reduction in 24-hour urine calcium excretion (Verdelli and Corbetta, 2017). This may also lead to hypercalcaemia. Although this hypercalcaemia is typically mild as a result of parathyroid hormone suppression, this can be significant in patients undiagnosed with primary hyperparathyroidism, prompting thiazide discontinuation (Tsvetov et al, 2017). However, Riss et al (2016) showed that use of thiazide diuretics did not increase serum calcium levels in patients with primary hyperparathyroidism.

In light of this, Tsvetov et al (2017) conducted a study to determine whether thiazides have a role in the management of patients with primary hyperparathyroidism. They found that hydrochlorothiazide use reduces hypercalciuria (from 427±176 mg/d off treatment to 251±114 mg/d on treatment, $P<0.001$) and may be beneficial in reducing serum parathyroid hormone levels (from 115±57 pg/dl off treatment to 74±36 pg/dl on treatment, $P<0.001$). This also suggested that most patients with primary hyperparathyroidism can safely take hydrochlorothiazide, as ongoing serum calcium monitoring revealed no significant effects on mean or maximal serum calcium levels (mean serum calcium levels 10.7±0.4 mg/dl off treatment and 10.5±1.2mg/dl on treatment, $P=0.4$; maximum serum calcium levels 11±0.5 mg/dl off treatment and 11±0.5 mg/dl on treatment, $P=0.8$) (Tsvetov et al, 2017). Nonetheless, the authors emphasised the need for careful serum calcium monitoring in all patients with primary hyperparathyroidism that start taking thiazides.

While further studies would be useful, Tsvetov et al (2017) found that hydrochlorothiazide (at doses from 12.5–50 mg/day) was safe and effective in reducing hypercalciuria and may be an option for preventing kidney stones in patients who fulfil the surgical indications for parathyroidectomy but are unfit for or refuse surgery.

Reducing fracture risk

Based on a meta-analysis of five cohort studies, Aung and Htay (2011) showed that thiazide use was associated with a reduction in the risk of hip fracture by 24%.

Solomon et al (2016) studied the effect of multiple classes of antihypertensive drugs on bone mineral density in women going through menopause and found that thiazide diuretics were the only antihypertensive medications associated with a lower annual percentage decline in bone mineral density, compared to women taking angiotensin-converting enzyme inhibitors and beta blockers.

Inactivation of the thiazide-sensitive sodium–chloride co-transporter as a result of genetic mutations or pharmacological inhibition with thiazide diuretics causes hypocalciuria and increased bone mineral density. Hsu et al (2015) found that mice with an inactivating homozygous mutation in the sodium–chloride co-transporter had increased intestinal absorption of calcium, significantly greater mineral apposition rate in their femurs in addition to increased trabecular bone volume, cortical bone thickness and bone mineral density.

Pierce and Perry (1998) found that at 35 days post fracture to the right tibia, mice who had received thiazide diuretics had higher bone mineral content than those who did not, suggesting that thiazide diuretics enhance bone mineral crystallisation.

Key points

- The effect of thiazide diuretics on parathyroid hormone levels is unclear.
- Thiazide diuretics should be discontinued for at least 1 week before evaluating serum and urine calcium and creatinine levels in patients being investigated for hypercalcaemia.
- A thiazide challenge test may be useful in distinguishing secondary hyperparathyroidism resulting from urinary calcium losses from normocalcaemic primary hyperparathyroidism in patients with concomitant elevated parathyroid hormone levels and hypercalciuria.
- In patients with primary hyperparathyroidism who are unfit for surgery, or fail or decline surgery and have hypercalciuria, nephrocalcinosis or nephrolithiasis, thiazide diuretics may be an option to reduce hypercalciuria.
- Thiazide diuretics have a beneficial effect on bone density and fracture risk reduction, but the duration of this is unclear.
- Further research is required to fully understand the roles of thiazide diuretics and their clinical implications in the diagnosis and management of primary hyperparathyroidism.

A study by Transbøl et al (1982) on postmenopausal women suggested that the slowing rate of bone loss is transient, with sustained bone mineral content seen in the first 6 months of thiazide use, followed by a decline in bone mineral density at the same rate as the placebo group thereafter. This contrasts with Ray et al's (1989) case-controlled study which found that men and women taking thiazides for 6 years or more had a significantly lower risk of hip fracture. LaCroix et al (1990) also reported that thiazide diuretic use was associated with a reduction in hip fracture risk by around 30%.

Surgical parathyroidectomy is the recommended treatment in patients with primary hyperparathyroidism who have osteoporosis and are surgical candidates, whereas bisphosphonates can be used in those who are unfit for surgery, or fail or decline surgery. Hence, as Tsvetov et al (2017) suggested, further research is required to assess whether thiazides may have a therapeutic role in reducing the risk of fracture in patients with primary hyperparathyroidism.

Conclusions

There is an interesting correlation between thiazide diuretics and the diagnosis and management of primary hyperparathyroidism. While a thiazide challenge test can help distinguish between normocalcaemic primary hyperparathyroidism and secondary hyperparathyroidism as a result of urinary calcium losses, thiazides can interfere with the diagnostic process of hypercalcaemia.

Thiazide diuretics reduce hypercalciuria and the risk of renal stone formation. This may be useful in patients who are not fit for surgery and have no other means to reduce the risk of renal calculi formation. On the other hand, thiazide diuretics increase the risk of hypercalcaemia in patients with primary hyperparathyroidism. Furthermore, an association between thiazide diuretic use and the reduced risk of hip fractures as well as a lower annual percentage decline in bone density has been reported. However, the duration of the latter effects has been questioned as some studies suggest that the effect on bone mineral density is transient. Given the current evidence regarding thiazide diuretics, further research would be beneficial to fully understand the significance of each role and its clinical implications.

Author details

[1]Department of Diabetes and Endocrinology, Mater Dei Hospital, Msida, Malta

[2]Department of Medicine, Mater Dei Hospital, Msida, Malta

Conflicts of interest

The authors declare that there are no conflicts of interest.

References

Afzal M, Kathuria P. Familial hypocalciuric hypercalcemia. Treasure Island (FL): StatPearls Publishing; 2023

Akbari P, Khorasani-Zadeh A. Thiazide diuretics. Treasure Island (FL): StatPearls Publishing; 2023

Aung K, Htay T. Thiazide diuretics and the risk of hip fracture. Cochrane Database Syst Rev. 2011;10:CD005185. https://doi.org/10.1002/14651858.CD005185

Bergsland KJ, Worcester EM, Coe FL. Role of proximal tubule in the hypocalciuric response to thiazide of patients with idiopathic hypercalciuria. Am J Physiol Renal Physiol. 2013;305(4):F592–F599. https://doi.org/10.1152/ajprenal.00116.2013

Bilezikian JP, Khan AA, Silverberg SJ et al. Evaluation and management of primary hyperparathyroidism: summary statement and guidelines from the fifth international workshop. J Bone Mineral Res. 2022;37(11):2293–2314. https://doi.org/10.1002/jbmr.4677

Bollerslev J, Rejnmark L, Zahn A et al. 2021 PARAT Working Group. European expert consensus on practical management of specific aspects of parathyroid disorders in adults and in pregnancy: recommendations of the ESE Educational Program of Parathyroid Disorders. Eur J Endocrinol. 2022;186(2):R33–R63. https://doi.org/10.1530/EJE-21-1044

Coe FL, Canterbury JM, Firpo JJ, Reiss E. Evidence for secondary hyperparathyroidism in idiopathic hypercalciuria. J Clin Invest. 1973;52(1):134–142. https://doi.org/10.1172/JCI107156

Corbetta S, Baccarelli A, Aroldi A et al. Risk factors associated to kidney stones in primary hyperparathyroidism. J Endocrinol Invest. 2005;28(4):122–128. https://doi.org/10.1007/BF03345354

Eisner BH, Ahn J, Stoller ML. Differentiating primary from secondary hyperparathyroidism in stone patients: the 'thiazide challeng'. J Endourol. 2009;23(2):191–192. https://doi.org/10.1089/end.2008.0567

Giles TD, Sander GE, Roffidal LE, Quiroz AC, Mazzu AL. Comparative effects of nitrendipine and hydrochlorothiazide on calciotropic hormones and bone density in hypertensive patients. Am J Hypertens. 1992;5(12_Pt_1):875–879. https://doi.org/10.1093/ajh/5.12.875

Hsu YJ, Yang SS, Cheng CJ et al. Thiazide-sensitive Na+ -Cl- cotransporter (NCC) gene inactivation results in increased duodenal Ca2+ absorption, enhanced osteoblast differentiation and elevated bone mineral density. J Bone Mineral Res. 2015;30(1):116–127. https://doi.org/10.1002/jbmr.2306

LaCroix AZ, Wienpahl J, White LR et al. Thiazide diuretic agents and the incidence of hip fracture. N Engl J Med. 1990;322(5):286–290. https://doi.org/10.1056/NEJM199002013220502

Muppidi V, Meegada SR, Rehman A. Secondary hyperparathyroidism. Treasure Island (FL): StatPearls Publishing; 2023

Nijenhuis T, Vallon V, van der Kemp AW et al. Enhanced passive Ca2+ reabsorption and reduced Mg2+ channel abundance explains thiazide-induced hypocalciuria and hypomagnesemia. J Clin Invest. 2005;115(6):1651–1658. https://doi.org/10.1172/JCI24134

Nowack R, Häfner MC, Reichel H, Schmidt-Gayk H, Ritz E. Subacute effects of thiazide administration on renal hemodynamics and calcium metabolism. Clin Investig. 1992;70(8):686–691. https://doi.org/10.1007/BF00180287

Pierce RO, Perry A. The effects of thiazide diuretics on bone mineral metabolism. J Natl Med Assoc. 1998;90(1):46–50

Prochaska M, Taylor E, Vaidya A, Curhan G. Low bone density and bisphosphonate use and the risk of kidney stones. Clin J Am Soc Nephrol. 2017;12(8):1284–1290. https://doi.org/10.2215/CJN.01420217

Ramakumar V, Kothari SS, Seth S, Kumar S. Reversible complete heart block due to hypercalcaemia. BMJ Case Rep. 2021;14(1):e238537. https://doi.org/10.1136/bcr-2020-238537

Ray WA, Griffin MR, Downey W, Melton LJ. Long-term use of thiazide diuretics and risk of hip fracture. Lancet. 1989;333(8640):687–690. https://doi.org/10.1016/s0140-6736(89)92205-8

Rejnmark L, Vestergaard P, Heickendorff L, Andreasen F, Mosekilde L. Effects of thiazide- and loop-diuretics, alone or in combination, on calcitropic hormones and biochemical bone markers: a randomized controlled study. J Intern Med. 2001;250(2):144–153. https://doi.org/10.1046/j.1365-2796.2001.00868.x

Reusz GS, Dobos M, Vásárhelyi B et al. Sodium transport and bone mineral density in hypercalciuria with thiazide treatment. Pediatr Nephrol. 1998;12(1):30–34. https://doi.org/10.1007/s004670050398

Riss P, Kammer M, Selberherr A et al. The influence of thiazide intake on calcium and parathyroid hormone levels in patients with primary hyperparathyroidism. Clin Endocrinol. 2016;85(2):196–201. https://doi.org/10.1111/cen.13046

Sadiq NM, Naganathan S, Badireddy M. Hypercalcemia. Treasure Island (FL): StatPearls Publishing; 2023

Sakhaee K, Nicar MJ, Glass K, Pak CY. Postmenopausal osteoporosis as a manifestation of renal hypercalciuria with secondary hyperparathyroidism. J Clin Endocrinol Metab. 1985;61(2):368–373. https://doi.org/10.1210/jcem-61-2-368

Shaker JL, Deftos L. Calcium and phosphate homeostasis. 2023. https://www.ncbi.nlm.nih.gov/books/NBK279023/ (accessed 9 October 2023)

Shinall MC, Dahir KM, Broome JT. Differentiating familial hypocalciuric hypercalcemia from primary hyperparathyroidism. Endocr Pract. 2013;19(4):697–702. https://doi.org/10.4158/EP12284.RA

Solomon DH, Ruppert K, Zhao Z et al. Bone mineral density changes among women initiating blood pressure lowering drugs: a SWAN cohort study. Osteoporos Int. 2016;27(3):1181–1189. https://doi.org/10.1007/s00198-015-3332-6

Transbøl I, Christensen MS, Jensen GF, Christiansen C, McNair P. Thiazide for the postponement of postmenopausal bone loss. Metabolism. 1982;31(4):383–386. https://doi.org/10.1016/0026-0495(82)90115-9

Tsvetov G, Hirsch D, Shimon I et al. Thiazide treatment in primary hyperparathyroidism-a new indication for an old medication? J Clin Endocrinol Metab. 2017;102(4):1270–1276. https://doi.org/10.1210/jc.2016-2481

Turner HE, Eastell R, Grossman A. Oxford desk reference endocrinology. Oxford: Oxford University Press; 2018

Verdelli C, Corbetta S. Mechanisms in Endocrinology: kidney involvement in patients with primary hyperparathyroidism: an update on clinical and molecular aspects. Eur J Endocrinol. 2017;176(1):R39–R52. https://doi.org/10.1530/EJE-16-0430

Walker MD, Bilezikian JP. Primary hyperparathyroidism. 2021. https://www.ncbi.nlm.nih.gov/books/NBK278923/ (accessed 9 October 2023)

Yacobi-Bach M, Serebro M, Greenman Y, Tordjman K, Stern N. Letter to the editor: thiazides are not inducers of PTH secretion: a comment on normocalcemic hyperparathyroidism. J Clin Endocrinol Metab. 2015;100(2):L27–L28. https://doi.org/10.1210/jc.2014-4065

Yeh MW, Ituarte PH, Zhou HC et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. J Clin Endocrinol Metab. 2013;98(3):1122–1129. https://doi.org/10.1210/jc.2012-4022

Zaheer S, de Boer I, Allison M et al. Parathyroid hormone and the use of diuretics and calcium-channel blockers: the multi-ethnic study of atherosclerosis. J Bone Miner Res. 2016;31(6):1137–1145. https://doi.org/10.1002/jbmr.2779

Zavatta G, Clarke BL. Normocalcemic hyperparathyroidism: a heterogeneous disorder often misdiagnosed? JBMR Plus. 2020;4(8):e10391. https://doi.org/10.1002/jbm4.10391