Article

Treatment of primary hypercalciuria

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Summary

Idiopathic hypercalciuria (HC) occurs in about 50% of patients with nephrolithiasis and is often associated with the fasting HC. While increasing the risk for stone formation HC may involve mineral metabolism and bone turnover, as a consequence of sustained negative calcium balance, despite increased intestinal absorption of calcium. Therapeutic options take account of this. Apart from dietary management, which is treated elsewhere, drugs so far used in HC patients include: thiazides, alkali, bisphosphonates, neutral potassium phosphate. Issues concerning mechanisms and treatment of some genetic HC are also discussed in this review.
Thiazides alone or in association with amiloride, reduce calcium excretion, revert external balance and protect bone from demineralisation. They act by increasing calcium reabsorption at the cortical segment of the distal tubule. Over long-term there is net retention of calcium, which results in a favourable impact on bone, as suggested by a number of epidemiology studies. Thiazides was also shown to exert direct effects on bone, by acting on osteoblast function. These studies strongly support thiazides use when negative calcium balance and enhanced bone resorption are suspected. Hypertensive patients with HC are also eligible, but no limitation to their extensive use exists.
Alkaline potassium citrate has a dual effect on HC: citrate anion strongly binds to calcium; alkalinisation expectedly reduces bone resorption. Thus both ionised and total calcium excretion are decreased by citrate. The same effects are shared by other alkaline compounds, such as potassium bicarbonate, which improved calcium balance, reduced bone resorption and increased bone formation in postmenopausal women. Potassium citrate was shown to induce similar effects in healthy menopausal women over a short-term course.
The well known effect of bisphosphonates on bone resorption will theoretically lower calcium excretion. Alendronate, prevented HC induced by prolonged bed-rest. Genetic hypercalciuric rats reduced calcium excretion on alendronate administration. Alendronate 10 mg/daily reduced both fasting and 24-hr calcium excretion in patients with fasting HC over a two-year follow-up.
Renal phosphate leak HC has been treated with neutral potassium phosphate. Daily dosages of 40 mmoles decreased urine calcium, by acting on both intestinal absorption and bone resorption, an effect consistent with a contribution of bone to the phosphate-depletion induced HC.
Genetic disorders associated with HC involve mutations of candidate genes including chloride channel 5 (CLCN-5), the calcium sensing receptor (CaR) and the paracellin-1 (PCLN-1). Studies performed in these subsets not only contributed to clarify mechanisms of the disease, but also help to understand the pathophysiology of HC. Treatment of these genetic HC was addressed by recent reports which used thiazides in Dent's syndrome, CaR and PCLN-1 mutations, vitamin D and synthetic human PTH in CaR, with encouraging results.

KEY WORDS: hypercalciuria, nephrolithiasis, thiazides, potassium citrate, bisphosphonates, potassium phosphate.

Introduction

Idiopathic hypercalciuria is the most frequent metabolic abnormality since up to 40 to 60% of patients with nephrolithiasis are hypercalciuric (1,2-5). Fasting hypercalciuria, accompanies idiopathic hypercalciuria in up to 50% of the patients (6). It is widely agreed that high calcium excretion may be causative for stone disease, because the higher calcium concentration, the higher the state of saturation with the calcium forming salts (7). However, a more general involvement of mineral metabolism, and in particular bone turnover, comes from the fact that virtually all of these patients tend to develop a negative external balance of calcium, because renal loss overtakes net calcium absorption at the intestine (8).
The mechanisms of hypercalciuria are complex and not fully clarified as yet, and this issue is the object of another article in the Journal. Anyway, a better understanding of the pathogenesis of hypercalciuria represents the basis of the different therapeutic options so far pursued, which will be the object of the present review. These are listed in Table I. The points concerning the dependence of calcium excretion on dietary factors will be omitted, being treated elsewhere in this issue.

Table I - Therapeutic options in primary hypercalciuria.

Diet and Fluid intake
Thiazides
Alkali
Bisphosphonates
Neutral Potassium Phosphate
Recent issues

Thiazide diuretics

The drugs of this class have been widely used in patients with calcium nephrolithiasis, more so in those presenting with idiopathic hypercalciuria (9-11). Hydrochlorothiazide, chlortalidone

(10) or trichlormethiazide, alone or in association with amiloride (11), induce a significant reduction of calcium excretion, revert external balance of calcium to positive (12), and protect bone from demineralisation (13-15). Thiazides are able to reduce calcium excretion by acting at the cortical segment of the distal tubule, where they increase calcium reabsorption. This mechanism is thought to ensue from contraction of extra-cellular fluids induced by these drugs (16). Prostaglandin E_2, which is likely involved in the pathogenesis of hypercalciuria, was suggested to be inhibited by thiazides (17). It has also been hypothesised that, over long-term therapy, they reduce both intestinal absorption (12,18) and bone resorption of calcium (19). Zerwekh et al. found that 50 mg of hydrochlorothiazide twice daily reduced fractional intestinal absorption of calcium from 0.68 to 0.56 in patients with renal leak hypercalciuria, but not in those with absorptive hypercalciuria, and this effect was attributed to a reduction of serum levels of calcitriol (18). Reduction of calcium intestinal absorption was also observed by Coe et al. in 7 patients with severe hypercalciuria after 3 and 6 months of either chlortalidone or trichlormethiazide: despite this, calcium retention improved because calcium loss decreased even more. No changes were seen in calcitriol and parathormone serum concentrations (12). Favus et al. carried out an experimental study on rats in which secondary hyperparathyroidism was induced by a low-calcium diet (20). They found that thiazides prevented the increase in PTH induced by low-calcium diet but not the increase in calcitriol nor intestinal calcium transport, and the drug caused no change in rats fed normal chow. Furthermore, in rats given exogenous calcitriol to stimulate intestinal calcium absorption, thiazides greatly reduced urine calcium excretion but did not alter intestinal calcium absorption (20).
The issue of calcium absorption and thiazides is important for the potential effect on intestinal absorption of oxalate, in that intestinal transport of the former influences the latter (21,22). Earlier reports of the effects of thiazides found a decrease in oxalate excretion (10), whereas others failed to confirm it (23). This topic has not so far been studied in more depth.
The positive calcium balance induced by long-term therapy with thiazides may have a favourable impact on bone. A number of epidemiology studies have addressed this issue, and found that the risk of hip fractures reduced by 30% and 50% over more than 2.5 and 6 years of therapy, respectively (13, 14). A rapid recovery of bone mass occurred in osteoporotic hypercalciuric men given thiazides (15). In a meta-analysis on 13 observational studies in which 22,600 subjects had extractable data on thiazides and fracture occurrence, current thiazide users of long duration were protected against hip fracture with a 20% reduction in risk, whereas short duration use did not (24). In a large survey conducted by U.S. on 83,728 women aged 36-61 at baseline and followed for 10 years, there was a 29% reduction in the risk of forearm fractures among current thiazide users, reaching 37% among women who had been using thiazides for 8 or more years. For hip fractures, thiazide use yielded a 31% reduction in the relative risk (25). In a recent 2-year prospective follow-up conducted on 136 women given hydrochlorothiazide 50 mg per day, urine calcium excretion and indices of bone turnover decreased in the thiazide group. DEXA bone mineral density improved in total body, mid- and ultradistal forearm and legs, but no effect was seen in the lumbar spine or femoral neck, leading Authors to conclude that thiazides are not an appropriate monotherapy for treating osteoporosis (26). In a prospective population-based cohort study, on 7,891 individuals 55 years of age, current use of thiazides for more than 1 year was associated with a lower risk for hip fracture, but this protective effect disappeared within 4 months after use was discontinued (27). The mechanisms of the beneficial effects of thiazides on bone may be not merely related to their ability to reduce urinary calcium, and direct effects on bone resorption were postulated. This effect is partly due to a reduction in PGE2 synthesis (17). Thiazides have specific effects on osteoblasts, because they reduce serum osteocalcin. *In vitro* studies on human osteoblast-like cell line showed hydrochlorothiazide dose-dependently inhibited 1,25-dihydroxyvitamin D_3-induced osteocalcin release and mRNA expression, independently of VDR or extracellular Ca^{2+} levels, and TNF-α induced production con macrophage CSF as well. This may explain its preventive role in bone loss rate (28,29).
The majority of the aforementioned studies support indications to thiazide use especially in the setting of hypercalciuria associated with negative calcium balance and enhanced bone resorption. Anyway, the former limitation of thiazides use to renal hypercalciuria was subsequently extended to any type of hypercalciuria, in both adults (30,10-13) and children (31). The favourable effects on stone recurrences obtained by using higher dosages, i.e. hydrochlorothiazide 50 mg twice daily (10) or chlortalidone 50 mg/day (32), were also confirmed with lower doses and even in the absence of a marked reduction of calcium excretion (1,33). The rationale for the use of lower dosages is to reduce the impact of side-effects, including hypotension, potassium wasting and hypopotassiemia, increase of plasma bicarbonate (and urate), and a consequent decrease in citrate excretion. The latter event may be as important as to offset the benefits related to the reduction of calcium excretion. It is agreed that some of these side-effects can be lessened by giving thiazides with amiloride (11), and by supplementing potassium citrate in the presence of hypocitraturia (34). Hypercalciuric patients presenting with hypertension may be especially eligible for thiazides (35).

Potassium citrate

Citrate supplementation, as alkaline potassium salt, was formerly introduced in the treatment of distal renal tubular acidosis (36) and subsequently extended to idiopathic hypocitraturic calcium nephrolithiasis (37). Regardless of the accompanying cation (sodium, potassium, magnesium) citrate salts exhibit direct effects on calcium excretion, acting by two distinct mechanisms: first, citrate anion is a strong ligand of calcium, and this will result in a decrease in free ionised calcium concentration (38); second, alkalinisation is expected to reduce bone resorption (39), thereby decreasing total calcium excretion.
The principal effect of citrate on calcium excretion is due to its ability to bind calcium, so that the calcium-citrate soluble complex accounts for by about 10 to 40% of total urinary calcium (Figure 1). Therefore, an increase in urinary citrate will result in a decrease in the fraction of free-ionised calcium, which is the

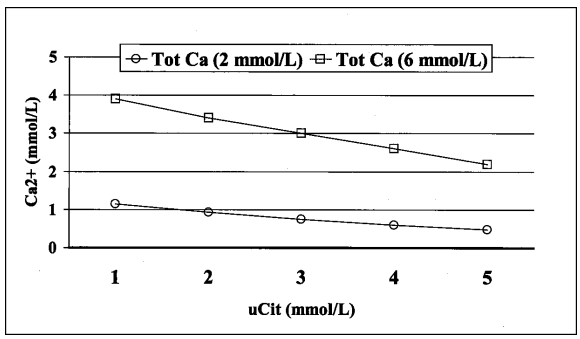

Figure 1 - Dependence of free ionised calcium on citrate in urine specimens at two different total calcium concentrations.

species thermodynamically important for the saturation of calcium forming salts (38).
The effect of potassium citrate upon the skeleton is shared by other alkaline salts, such as potassium bicarbonate. In fact, in postmenopausal women, the oral administration of potassium bicarbonate, at a dose sufficient to neutralise endogenous acid, improved calcium balance, by reducing calcium excretion, through a reduction of bone resorption and an increase in the rate of bone formation (40). In a prospective short-term study, alkaline mineral water induced a significant reduction in the biochemical markers of bone resorption (9). There also are recent reports of a specific effect of potassium intake on calcium excretion, because it has been found that potassium deficiency increases, whereas potassium supplementation as either citrate or bicarbonate or chloride salts, decreases calcium excretion (41). Potassium citrate, given to healthy menopausal women decreased net acid excretion and concurrently decreased markers of bone resorption (Figure 2). Percent variations of urine citrate were inversely related to those of deoxypyridinolines and hydroxyproline, whereas calcium excretion exhibited only minor decreases (42).

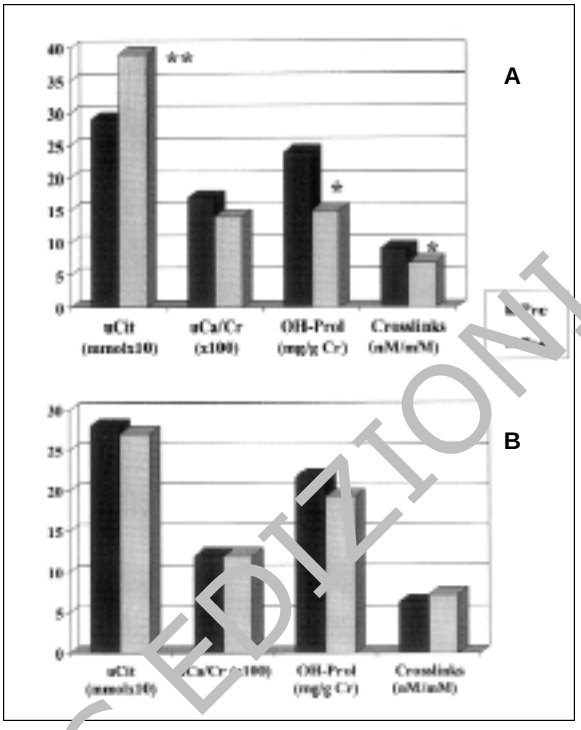

Figure 2 - Effetcs of a three-month course of potassium citrate on bone metabolism and calcium excretion in post-menopausal women. Treated women (panel A) are compared to untreated ones (panel B) (**p<0.001 vs baseline; **p<0.01 vs baseline).

Bisphosphonates

Bisphosphonates are widely used to prevent osteoporosis and, among these, alendronate and risedronate, exhibit a favourable efficacy/safety profile over long-term use (43-45). Theoretically, if increased bone resorption partly explained idiopathic hypercalciuria, it follows that drugs capable of reducing the rate of bone turnover should also have some effect on calcium excretion. Alendronate, 20 mg daily, had been shown to prevent hypercalciuria and the calcium-stone forming propensity induced by prolonged bed-rest (46). Independently of immobilization, genetic hypercalciuric rats reduced both calcium excretion and urine saturation with calcium salts upon alendronate administration (47). The effects of bisphosphonates on calcium excretion was studied in the phosphate depletion-induced hypercalciuria, which is referred to as being caused by increased efflux of calcium from bone. Phosphate depleted rats developed hypophosphatemia, hypercalcemia and hypercalciuria, but failed to respond to pamidronate, despite an improved bone histology (48).
Recently we have reported similar results in patients with fasting hypercalciuria who had been given alendronate 10 mg/daily and re-studied after a three-month course. There was a significant decrease in both fasting and 24-hour calcium excretion and, consequently, a 43% reduction in urine saturation with calcium oxalate (49). These changes were obtained in the face of normal levels of plasma calcium and only minor and transient increases in serum PTH, and maintained over a two-year follow-up (Figure 3). From these results bisphosphonates appear as promising new tools in the management of hypercalciuria, namely in the fasting hypercalciuria or in patients with biochemical (and clinical) evidence of increased bone resorption.

Neutral potassium phosphate

An association between hypercalciuria and renal phosphate leak was first described by Bordier et al. (50), who speculated that a primary defect of phosphate reabsorption at the proximal

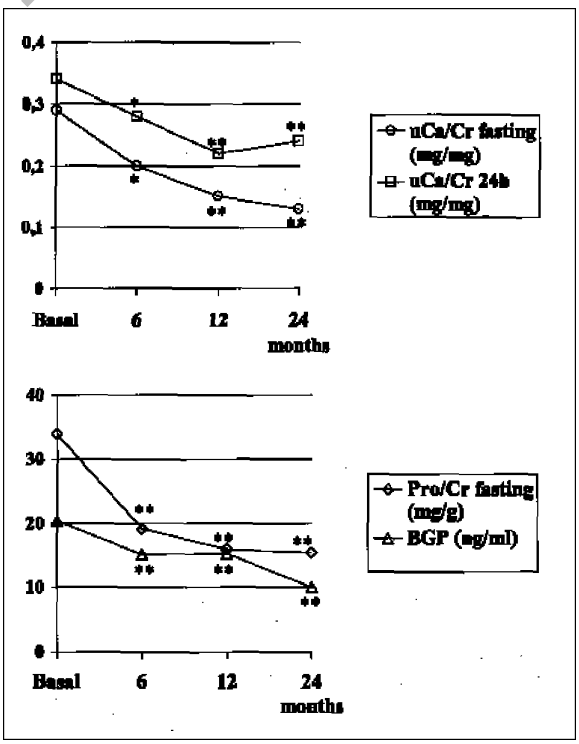

Figure 3 - Long-term effects of Alendronate, 10 mg daily, on bone resorption (lower panel) and calcium excretion (upper panel) in hypercalciuric patients. (* p<0.05; ** p<0.01 vs basal values).

Table II - Genetic hypercalciuria.

Protein	Gene	Transmission	Disease
Chloride channel 5 (ClC-5)	CLCN5	X-linked	Dent's syndrome and related disorders
Ca^{2+} Sensing* Receptor	CaR	Autosomal dominant	Familial hypocalcemic hypercalciuria (FHH)
Paracellin-1	PCLN-1	Autosomal recessive	Familial hypomagnesiemic hypercalciuria and nephocalcinosis (FHHNC)

* Mutation inducing gain of function

renal tubule could be responsible for hypophosphatemia, activation of the renal 1α-25$(OH)_2$ vitamin D_3 hydroxylase and partial inhibition of PTH secretion. The associated hypercalciuria would ensue from both increased intestinal absorption and decreased tubular resorption of calcium. That this subtype of hypercalciuria can be of clinical significance was confirmed by a recent report in which 19% of 207 stone formers had a TmPi of less than 0.63 mmol versus 5% of controls; daily calcium excretion was higher in stone formers, more so if they had reduced TmPi (51). It was also suggested that this hypothetical tubular defect could involve the type IIa Na^+-phosphate cotransporter through mutations of the encoding gene Npt2. In fact, knock-out mice for the Npt2 gene [Npt2(–/–)] exhibited increased urinary Pi excretion, hypophosphatemia, elevation in 1,25-$(OH)_2$ vitamin D, hypercalcemia, hypercalciuria and low PTH (52). Partially deficient mice [Npt2(+/–)] had similar though milder changes. It was suggested these features be typical of patients with hereditary hypophosphatemic rickets with hypercalciuria (HHRH), and that patients with phosphate leak hypercalciuria could have heterozigous mutations of the Npt2 gene (51,53). However, others have denied that Npt2 mutations could be responsible for both diseases (54,55).
Phosphate supplementation, as neutral slow-release potassium phosphate, was given to patients with absorptive hypercalciuria. In a short-term study daily dosages corresponding to 40 mmoles of phosphate and 63.5 mmoles of potassium decreased 24-hr and fasting urinary calcium by 25% and 43%, respectively (56). These marked changes were not simply attributable to a decrease in intestinal absorption of calcium, which only fell by 6%, but were associated to a clear-cut decrease in bone resorption, as suggested by the significant decline in markers of bone turnover. These effects are consistent with the aforementioned contribution of bone resorption to the phosphate-depletion induced hypercalciuria (48). The efficacy of phosphate supplementation to restore mineral metabolism are still debatable since, in the presence of renal leak, an increase in phosphate disposal could result in phosphaturia. In mice Npt2(–/–) phosphate supplementation did not prevent hypercalciuria and renal calcification, unless associated to 1a-hydroxylase gene ablation (57). If this also applied to humans, treatment of phosphate leak should not only include phosphate supplies but also inhibition of calcitriol synthesis.

Recent issues on treatment of genetic hypercalciuria

The amazing advances in molecular genetics have also involved hypercalciuria, and at least three candidate genes were shown to arbour mutations leading to altered calcium excretion. The chloride channel 5 (ClC-5), the calcium sensing receptor and the paracellin-1 are proteins encoded by corresponding genes, whose mutations causing either loss or gain of function, lead to hypercalciuric syndromes (Table II). Transfection or gene-disruption studies with these genes not only contribute to clarify mechanisms of the underlying diseases, but also help to understand the pathophysiology of idiopathic hypercalciurias.
Recent reports have addressed the issue of treatment of genetic hypercalciurias, namely in the course of Dent's syndrome and familial hypocalcemic hypercalciuria.
The mechanism leading to hypercalciuria in Dent's syndromes is as yet not fully elucidated, in that both intestinal hyperabsorption and renal leak could contribute. Chlorthalidone, but not amiloride, was shown to reduce both calcium excretion and calcium oxalate and calcium phosphate supersaturation in Dent's syndrome, yielding similar results as in patients with idiopathic hypercalciuria (58). These results led authors to conclude that the hypocalciuric response to thiazides indicates that inactivation of the ClC-5 does not impair calcium transport in the distal convoluted tubule and that thiazides should be effective in reducing the risk of kidney stone recurrence in these patients.
Different approaches were tried in patients with CaR mutations with gain of function. These patients may present with hypocalcemia of various severity, some of them presenting with major clinical signs of hypocalcemia. The classical treatment with active vitamin D derivatives, while relieving hypocalcemic symptoms, induced significant increases in calcium excretion with an attendant risk of nephrocalcinosis (59). More recently, synthetic human PTH-(1-34) was shown to provide a safe and effective alternative to calcitriol therapy, able to maintain normal serum calcium levels without hypercalciuria (60). Similar encouraging results have been reported in two such patients by using hydrochlorothiazide (1 mg/kg), which reduced urinary calcium excretion and maintained serum calcium concentrations near the lower limit of normal, allowing the vitamin D doses to be reduced, while alleviating symptoms (61).
Finally, magnesium salts and thiazides were used to treat patients with FHHNC (see Table II) caused by paracellin-1 mutations. While being of some efficacy to correct biochemical changes, treatment did not prevent, however, progression to chronic renal failure, which is a feature of this disease (62).

References

1. Coe FL, Parks JH, Asplin JR. The pathogenesis and treatment of kidney stones. New Engl J Med. 1992; 327:1141-52.
2. Pak CYC, Ohata M, Lawrence EC, Snyder W. The hypercalciurias: causes, parathyroid functions and diagnostic criteria. J Clin Invest. 1974;54:387-400.
3. Pak CYC, Britton F, Peterson R, Ward D, Northcutt C, Breslau NA, Mc Guire J, Sakhaee, Bush S, Nicar M, Norman D, Peters P. Ambulatory evaluation of nephrolithiasis: Classification, clinical presentation and diagnostic criteria. Am J Med. 1980;69:19-30.
4. Preminger GM: The metabolic evaluation of patients with recurrent nephrolithiasis: A review of comprehensive and simplified ap-

proaches. J Urol. 1989;141:760-763.
5. Lemann J Jr, Gray RW. Idiopathic hypercalciuria. J Urol. 1989; 141:715-719.
6. Marangella M. Metabolic evaluation of calcium nephrolithiasis. J Nephrol. 1995;8:179-184.
7. Marangella M, Petrarulo M, Daniele PG, Sammartano S LithoRisk: A software for calculating and visualising nephrolithiasis risk profiles.G Ital Nefrol. 2002;19:693-698.
8. Coe FL, Favus MJ. Disorders of stone formation. In: Brenner BM & Rector FC eds. W.B. Saunders Co. Philadelphia, 1986,1403-1442.
9. Marangella M, Vitale C, Petrarulo M, Rovera L, Dutto F. Effects of mineral composition of drinking water on risk for stone formation and bone metabolism in idiopathic calcium nephrolithiasis. Clin Sci. 1996;91:313-318
10. Yendt ER, Cohanim M. Prevention of calcium stones with thiazides. Kidney Int. 1978;13:397.
11. Maschio G, Tessitore N, D'Angelo A et al. Prevention of calcium nephrolithiasis with low-dose thiazide, amiloride and allopurinol. Am J Med. 1981;71:623-626.
12. Coe FL, Parks JH, Bushinsky DA, Langman CB, Favus MJ. Chlorthalidone promotes mineral retention in patients with idiopathic hypercalciuria. Kidney Int. 1988;33:1140-1146.
13. Lacroix AZ, Wienpahl J, White LR et al. Thiazide diuretic agents and the incidence of hip fracture. N Engl J Med. 1990;322:286-290.
14. Herings RM, Stricker BH, de Boer A, Bakker A, Sturmans F, Stergachis A. Current use of thiazide diuretics and prevention of femur fractures. J Clin Epidemiol. 1996;49:115-119.
15. Adams JS, Song CF, Kantorovich V. Rapid recovery of bone mass in hypercalciuric, osteoporotic men treated with hydrochlorothiazide. Ann Intern Med. 1999;130:658-560.
16. Costanzo LS, Weiner IM. On the hypocalciuric action of chlorothiazide.J Clin Invest. 1974;54:628-637.
17. Calò L, Cantaro S, Marchini F et al. Is hydrochlorothiazide-induced hypocalciuria due to inhibition of prostaglandin E2 synthesis? Clin Sci. 1990;78:321-325.
18. Zerwekh JE, Pak CYC. Selective effects of thiazide therapy on serum 1,25-dihydroxyvitamin D and intestinal calcium absorption in renal and absorptive hyercalciuria. Metabolism. 1980;29:13-17.
19. Lemann J Jr, Gray RW, Mayerhofer W, Cheung HS. Hydrochlorothiazide inhibits bone resorption in men despite experimentally elevated serum 1,25-dihydroxyvitamin D concentrations. Kidney Int. 1985;28:951-956.
20. Favus MJ, Coe FL, Kathpalia SC, Pollat A, Sen PK, Sherwood LM. Effects of chlorothiazide on 1,25-dihydroxyvitamin D3, parathyroid hormone, and intestinal calcium absorption in the rat. Am J Physiol. 1982;242:G575-81.
21. Messa P, Marangella M, Pasanin A, Codardini M, Cruciatti A, Turrin D, Filiberto Z, Minoi G: Different dietary calcium intake and relative supersaturation of calcium oxalate in the urine of patients forming renal stones. Clin Sci. 1997;93:257-263.
22. Holmes RP, Goodman HO, Assimos DG. Contribution of dietary oxalate to urinary oxalate excretion. Kidney Int. 2001;59:270-276.
23. Hoyer J, Roulin F, Haldimann B. Short-term effect of thiazides on magnesium and calcium metabolism and secondarily on that of phosphorus, uric acid, oxalate and cyclic AMP. Nephrologie. 1983; 4:60-63.
24. Jones G, Nguyen T, Sambrook PN, Eisman JA. Thiazide diuretics and fractures: can meta-analysis help?J Bone Miner Res. 1995; 10:106-111.
25. Feskanich D, Willett WC, Stampfer MJ, Colditz GA. A prospective study of thiazide use and fractures in women. Osteoporos Int. 1997;7:79-84
26. Reid IR, Ames RW, Orr-Walker BJ, Clearwater JM, Horne AM, Evans MC, Murray MA, McNeil AR, Gamble GD. Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: a randomized controlled trial. Am J Med. 2000;109:362-70.
27. Schoofs MW, van der Klift M, Hofman A, de Laet CE, Herings RM, Stijnen T, Pols HA, Stricker BH.Thiazide diuretics and the risk for hip fracture. Ann Intern Med. 2003;139:476-482.
28. Aubin R, Menard P, Lajeunesse D. Selective effect of thiazides on the human osteoblast-like cell line MG-63. Kidney Int. 1996; 50:1476-1482.
29. Lajeunesse D, Delalandre A, Guggino SE. Thiazide diuretics affect osteocalcin production in human osteoblasts at the transcription level without affecting vitamin D3 receptors. J Bone Miner Res. 2000;15:894-901.
30. Pak CYC. Medical prevention of renal stone disease. Nephron 1999;81 (suppl 1): 60-65.
31. Hymes LC, Warshaw BL. Thiazide diuretics for the treatment of children with idiopathic hypercalciuria and hematuria. J Urol. 1987;138:1217-1219.
32. Ettinger B, Citron JT, Livermore B, Dolman LI. Chlorthalidone reduces calcium oxalate calculus recurrence but magnesium hydroxide does not. J Urol. 1989;139:679-684.
33. Jaeger P, Portmann L, Jacquet AF, Bugnon M, Burckhardt P.Optimal dosage of chlorthalidone in the prevention of the recurrence of nephrolithiasis is 25 mg per day. Schweiz Med Wochenschr 1986;116:305-308.
34. Nicar MJ, Peterson R, Pak CYC. Use of potassium citrate as potassium supplement during thiazide therapy of calcium nephrolithiasis. J Urol. 1984;131:433-433.
35. Quereda C, Ortola L, Sabater J, Navarro-Antolin J, Villafruela JJ, Ortuno J. Urinary calcium excretion in treated and untreated essential hypertension. J Am Soc Nephrol. 1996;7:1058-1065.
36. Sakhaee K, Nicar M, Hill K, Pak CY. Contrasting effects of potassium citrate and sodium citrate therapies on urinary chemistries and crystallization of stone-forming salts. Kidney Int. 1983;24:348-357.
37. Pak CY, Fuller C. Idiopathic hypocitraturic calcium-oxalate nephrolithiasis successfully treated with potassium citrate. Ann Intern Med. 1986;104:33-37.
38. Marangella M, Daniele PG, Ronzani M, Sonego S, Linari F. Urine saturation with calcium salts in normal subjects and idiopathic calcium stone formers estimated by an improved computer model system. Urol Res 1985;13:189-193
39. Lemann J Jr, Bushinsky DA, Hamm LL Bone buffering of acid and base in humans. Am J Physiol. (Renal Physiol) 2003;285:F811-32.
40. Sebastian A, Harris ST, Ottaway JH, Todd KM, Morris RC Jr. Improved mineral balance and skeletal metabolism in postmenopausal women treated with potassium bicarbonate. N Engl J Med. 1994;330:1776-1781.
41. Lemann JJr. Relationship between urinary calcium and net acid excretion as determined by dietary protein and potassium. A review. Nephron. 1999; 81 (suppl. 1):18-25.
42. Marangella M, Di Stefano M, Casalis S, Berutti S, D'Amelio P, Isaia GC. Effects of Potassium Citrate Supplementation on Bone Metabolism. Calcif Tissue Int. 2004.
43. Tucci JR, Tonino RP, Emkey RD, Peverly CA, Kher U, Santora AC. for the U.S. Alendronate Phase III Osteoporosis treatment study group. Am J Med. 1996;101:488-501.
44. Harris ST, Watts NB, Genant HK, et al. for the VERT Study Group. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with post-menopausal osteoporosis. A randomized controlled trial. JAMA. 1999;282:1344-1352.
45. Sorensen OH, Crawford GM, Mulder H, Hosking DJ, Gennari C, Mellstrom D, Pack S, Wenderoth D, Cooper C, Reginster JY. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. Bone. 2003;32:120-126.
46. Ruml LA, Dubois SK, Roberts ML, Pak CY. Prevention of hypercalciuria and stone-forming propensity during prolonged bedrest by alendronate. J Bone Miner Res. 1995;10:655-662.
47. Bushinsky DA, Neumann KJ, Asplin J, Krieger NS. Alendronate decreases urine calcium and supersaturation in genetic hypercalciuric rats.Kidney Int. 1999;55:234-234.
48. Jara A, Lee E, Stauber D, Moatamed F, Felsenfeld AJ, Kleeman CR. Phosphate depletion in the rat: effect of bisphosphonates and the calcemic response to PTH. Kidney Int. 1999;55:1434-1443.

49. Vitale C, Marangella M, Isaia GC, Petrarulo M, Rovera L, Ramello A. The effects of alendronate on urine biochemistry and mineral metabolism in stone formers with fasting hypercalciuria. It J Min Electr Metab. 1998;12:5-8.
50. Bordier P, Ryckewart A, Gueris J, Rasmussen H. On the pathogenesis of so-called idiopathic hypercalciuria. Am J Med. 1977; 63:398-409.
51. Prié D, Ravery V, Boccon-Gibod L, Friedlander G. Frequency of renal phosphate leak among patients with calcium nephrolithiasis. Kidney Int. 2001;60:272-276.
52. Beck L, Karaplis AC, Amizuka N, Hewson AS, Ozawa H, Tenenhouse HS. Targeted inactivation of Npt2 in mice leads to severe renal phosphate wasting, hypercalciuria, and skeletal abnormalities. Proc Natl Acad Sci USA. 1998;95:5372-5377.
53. Chau H, El-Maadawy S, McKee MD, Tenenhouse HS. Renal calcification in mice homozygous for the disrupted type IIa Na/Pi cotransporter gene Npt2. J Bone Miner Res. 2003;18:644-657.
54. van den Heuvel L, Op de Koul K, Knots E, Knoers N, Monnens L. Autosomal recessive hypophosphataemic rickets with hypercalciuria is not caused by mutations in the type II renal sodium/phosphate cotransporter gene. Nephrol Dial Transplant. 2001;16:48-51.
55. Virkki LV, Forster IC, Hernando N, Biber J, Murer H. Functional characterization of two naturally occurring mutations in the human sodium-phosphate cotransporter type IIa. J Bone Miner Res. 2003;18:2135-2141.
56. Breslau NA, Heller HJ, Reza-Albarran AA, Pak CYC. Physiological effects of a slow-release potassium phosphate for absorptive hypercalciuria: A randomized double-blind trial. J Urol. 1998;160: 664-668.
57. Tenenhouse HS, Gauthier C, Chau H, St-Arnaud R. 1{alpha}-Hydroxylase gene ablation and Pi supplementation inhibit renal calcification in mice homozygous for the disrupted Na/Pi cotransporter gene Npt2a. Am J Physiol Renal Physiol. 2004;286:F675-F681.
58. Raja KA, Schurman S, D'Mello RG, Blowey D, Goodyer P, Va[illegible] Why S, Ploutz-Snyder RJ, Asplin J, Scheinman SJ. Responsiveness of Hypercalciuria to Thiazide in Dent's Disease. J Am Soc Nephrol. 2002;13:2938-2944.
59. Lienhardt A, Bai M, Lagarde JP, Rigaud M, Zhang Z, Jia[illegible] Y, [illegible] tler ML, Brown EM, Garabedian M. Activating mutations of the calcium-sensing receptor: management of hypocalcemia. J Clin Endocrinol Metab. 2001;86:5313-5323.
60. Winer KK, Ko CW, Reynolds JC, Dowdy A, Keil [illegible], Peterson D, Gerber LH, McGarvey C, Cutler GB Jr. Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. J Clin Endocrinol Metab. 2003;88:4214-4220.
61. Sato K, Hasegawa Y, Nakae [illegible], Nagao K, Takahashi I, Tajima T, Shinohara N Fujieda K. Hydrochlorothiazide Effectively Reduces Urinary Calcium Excretion in Two Japanese Patients with Gain-of-Function Mutations of the Calcium-Sensing Receptor Gene. J Clin Endocr Metab. 2002;87:3068-3073.
62. Weber S, Schneider L, Peters M, Misselwitz J, Ronnefarth G, Boswald M, Bonzel KE, Seeman T, Sulakova T, Kuwertz-Broking E, Gregoric A, Puccoux JB, Tasic V, Manz F, Scharer K, Seyberth HW, Konrad M. Novel paracellin-1 mutations in 25 families with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. J Am Soc Nephrol. 2001;12:1872-1881.