Article

# Kidney complications in primary hypercalciuria

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**Summary**

**Prevalence of hypercalciuria is markedly increased in patients with calcium kidney stones, and recently it has been demonstrated that the risk to produce stones is positively related with the levels of calcium excretion in general population. The stone-promoting effect of hypercalciuria depends on the unusually high calcium concentrations in urine and tubular fluid which favor calcium salt precipitation. However, the specific role of calcium in the pathogenetic pathway leading to stone formation has not been elucidated and it is unclear whether initial events of this process develop in tubules or in papillary interstitium.**
**Nephrocalcinosis occurs in the course of many hereditary or acquired disorders having hypercalciuria as the common alteration and can progressively damage kidney function. In spite of the relevance of hypercalciuria for nephrocalcinosis, the specific effect of calcium in its development is yet unknown.**
**An increased frequency of hypercalciuria has also been recorded among patients with arterial hypertension. It has been hypothesized that a body calcium deficiency is induced by hypercalciuria and leads to the elevation of blood pressure. This may be true in a subgroup of patients, while hypercalciuria is likely to occur more commonly in patients with volume-dependent hypertension.**
**Irrespective of its possible causal role, hypercalciuria may predict individual susceptibility to stones, nephrocalcinosis or arterial hypertension. Measurement of 24 hour calcium excretion could become an instrument to identify subjects predisposed to these disorders.**

*KEY WORDS: nephrolithiasis, nephrocalcinosis, hypercalciuria.*

## Introduction

Primary hypercalciuria is a defect of calcium metabolism, characterized by increased 24 hour urinary calcium excretion which is not justified by any apparent metabolic alteration (1). Its prevalence is 5-10% in the general population (1), but is significantly higher in patients with calcium kidney stones (2), nephrocalcinosis (3), arterial hypertension (4) and osteoporosis (5).
Primary hypercalciuria has a familial distribution displaying a complex transmission pattern due to a polygenic substrate (6). In addition to the family history, large body mass and high intake of animal proteins and salt predispose to hypercalciuria (7, 8). Therefore, primary hypercalciuria appears as a multifactorial disorder determined by the interaction of different genetic and environmental factors (Fig. 1).
Urinary wastage of calcium can give rise to problems maintaining proper calcium balance; whereas, high calcium concentration in urine may predispose to nephrolithiasis and nephrocalcinosis.

## Kidney as a cause of primary hypercalciuria

In most patients, primary hypercalciuria results from an increase of intestinal calcium absorption (absorptive hypercalciuria) (2,9). In less than 5% of patients, primary hypercalciuria may be caused by a primary defect in tubular calcium reabsorption (renal hypercalciuria) (2,10). These different forms of hypercalciuria are clinically distinguished with the measurements of fasting calcium excretion and plasma PTH. In absorptive hypercalciuria, fasting calcium excretion is normal, while circulating levels of PTH are low. In renal hypercalciuria, both fasting calcium excretion and circulating PTH are high (10). In spite of these simple criteria, the real mechanisms leading to hypercalciuria remain unclear and around one-third of patients remain unclassifiable because they exhibit fasting hypercalciuria and normal plasma PTH (10). Furthermore, contrarily to expectations, patients with absorptive hypercalciuria often have a deficit in bone mineral density, similar to that observed in renal hypercalciuria (11,12). Recently, we found that hypercalciuric stone-forming women with low bone mineral density at ver-

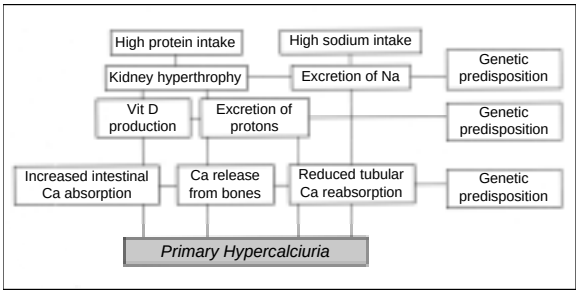


Figure 1 - Primary hypercalciuria is as a multifactorial disorder determined by the interaction of different genetic and environmental factors. Protein and sodium excess in diet increases urinary calcium excretion through different mechanisms. Genetic factors work at different phenotype levels and make hypercalciuric subjects more sensitive to stimuli inducing calcium excretion.

tebral sites presented the highest values of intestinal calcium absorption (11). This observation suggests that the defect causing hypercalciuria could be expressed in bones and intestine, where it could activate calcium absorption and bone metabolism and ultimately increase calcium excretion. Many proteins with a relevant role in calcium metabolism, like calcium-sensing receptor, vitamin D receptor or calcium pump, are expressed in bone, tubular and enteral cells. In case of their alteration, the effect on calcium excretion should result from the combination of their influences in bones, intestine and kidney. Therefore, in some groups of patients, pathogenesis of hypercalciuria could be more complex than proposed till now.

**Urinary alterations associated to primary hypercalciuria**

Increased excretions of sodium, sulphate, urate, urea and phosphate may be found in hypercalciuric patients and also in their relatives and were justified with a high dietary intake of these substances or their precursors (13). Further studies exploring the effect of nutrients on ion excretion displayed that animal proteins and sodium are important determinants of urinary calcium and that their excess in diet increases the values of excreted calcium (7,8,14,15).
Dietary sodium load favors excretion of calcium by a reduction of its tubular reabsorption (7,14), but this effect can manifest itself only when sodium is ingested as chloride salt, whereas it does not occur after a sodium-bicarbonate load (16).
A diet rich in animal proteins can increase the urinary excretion of urea, urate, sulphate, protons and calcium (15). Chronic load of acids, secondary to the catabolism of methionine and other acid amino acids, is able to decrease tubular calcium reabsorption and to release calcium ions from bone tissue, thus contributing to the increase of calcium excretion (14). In addition, chronically high protein intake may induce renal hypertrophy, which may up-regulate calcitriol synthesis. The consequent activation of intestinal calcium absorption and inhibition of PTH secretion may result in the development of hypercalciuria (8, 14).
All these findings suggest that chronic overconsumption of sodium-chloride and animal proteins predisposes to hypercalciuria. However, it remains unexplained why only some subjects can abnormally increase their calcium excretion as a consequence of a large ingestion of proteins and sodium-chloride. It is likely that genetic factors make hypercalciuric subjects more sensitive to stimuli inducing calcium excretion (Fig. 1).

**Hypercalciuria and calcium stone production**

Kidney stone disease may be considered as the main complication of hypercalciuria. Despite the amount of research, the first evidence that hypercalciuric subjects are predisposed to kidney stones was recently provided in a work, displaying that the risk to produce stones increased with calcium excretion in general population (17). Previous studies had limited their observation to the higher frequency of hypercalciuria in calcium stone forming patients and the larger calcium excretion in relapsing compared to non-relapsing stone formers (18).
In spite of these findings, the real role of calcium in stone formation has not been yet understood. Calcium stone-promoting activity may be due to the effect of calcium ions on urinary stability and saturation for calcium salts. However, when tested in vitro, the effect of calcium ions on the activity product of calcium-oxalate or calcium-phosphate was much less remarkable than that of phosphate, oxalate or water; thus, calcium concentration did not appear as the main determinant of salt solubility (19). Therefore, other aspects of calcium activity in stone formation have been explored. It was observed that the intrinsic urinary power to inhibit salt precipitation decreased when calcium was added to urine. This effect was attributed to calcium-induced alterations in molecular structure of Thamm-Horsfall protein, that reduced its efficacy to inhibit calcium-oxalate and calcium-phosphate crystal nucleation and growth (20).
Uncertainty about the role of calcium is also justified by the fact that the pathogenetic mechanism for stone production is unknown. The current theories hypothesize that initial events in stone formation can develop in tubules or, alternatively, in papillary interstitium. According to the tubular theory (Fig. 2), a stone can develop from crystal agglomerates retained within the lumen of a renal tubule (21). Physical-chemical characteristics of tubular fluid can promote the precipitation of calcium-phosphate within the ascending Henle's loop and calcium-oxalate in the collecting tubule (21). Crystals can grow and aggregate in supersaturated fluids and can be retained within the tubular lumen due to their capability to adhere to the tubular wall. Studies in animals showed that oxalate, under the form of ions or crystals, can cause tubular cell injury, necrosis or apoptosis with release of cell debris in tubular lumen and exposure of basement membrane to the tubular fluid. These events may be crucial for macroaggregate development and stone formation, because crystals can easily attach to the injured tubular wall and calcium-oxalate can precipitate on cell debris, especially membrane fragments rich of phospholipids, even in the presence of stable urine (21-23). The final pathway for stone production may be the retention of a crystal macroagglomerate within papillary Bellini's ducts, which may become a stone after ulceration of the papilla and its exposition to the urinary tract (24).
The alternative and recently renewed theory hypothesizes that papillary interstitium is the place where kidney stone is produced (24,25). Histological studies showed that calcium phosphate deposits (Randall's plaques) are typically found in papillary interstitium of patients with idiopathic calcium kidney stones (25). These plaques apparently originated from the basement membrane of thin descending loops of Henle's loop and developed into interstitium surrounding primarily tubules, vasa recta and Bellini's ducts. They were suburothelial, but could erode urothelium and erupt into calices (24), becoming an area where a calcium oxalate stone may develop. No intra-

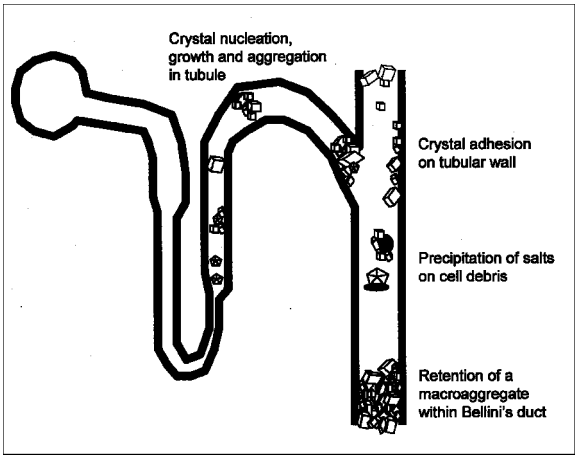


Figure 2 - The tubular theory hypothesizes that a stone can develop from crystal agglomerates retained within the tubular lumen. A nodular macroaggregate retained in a Bellini's duct may become a stone after ulceration of the papilla. Different steps in stone formation are described in the figure.

cellular or subcellular crystals were observed at kidney microscopic examination (25). Deposits were composed by hydroxyapatite with a small component of calcium carbonate.
In the same study, histological analysis of kidney papilla was also performed in patient with stones secondary to ileo-intestinal by-pass (25). Nodular apatite aggregates were detected within collecting ducts and were associated to cell injury, while no deposits were found on tubular basement membrane. Therefore, these different papillary pictures suggest that an interstitial stone pathogenesis occurs in patients with idiopathic calcium stones and a tubular pathogenesis in those with ileo-intestinal by-pass.
These two theories do not describe the role of hypercalciuria in stone production. Although not generally acknowledged, it is likely that its role depends on calcium concentrations in urine or renal interstitial fluid, which change in function of the calcium load provided by foods. Thus, calcium stone promoting activity may be enhanced after food intake, when the amount of filtered calcium and its tubular load raise. Postprandial overload may increase delivery of calcium to distal tubule; in outer medulla, calcium ions are reabsorbed and then carried into deep medulla by vasa recta (25). In hypercalciuric patients, this process occurs in the presence of unusually high calcium concentration and much more calcium may reach papilla. In addition to calcium, also a tubular overload of phosphate occurs after a meal, so that the stability of fluids for calcium and phosphate may be impaired in papillary interstitium or tubules (25). The formation of a Randall's plaque or a nodular magroaggregate in Bellini's duct may start the final process of stone formation, but it remains unexplained how calcium-oxalate stones may develop from interstitial hydroxyapatite or tubular calcium-phosphate deposits (21-23).

**Hypercalciuria and nephrocalcinosis**

Renal deposition of calcium-phosphate or calcium-oxalate results in nephrocalcinosis. This disorder is more frequently found in children and preterm newborns and deposits are more frequently composed by apatite and begins within medulla. In rare patients with primary hyperoxaluria (type 1 or 2) deposits are cortical and composed by calcium-oxalate.
Nephrocalcinosis may occur in the course of many hereditary tubular disorders having hypercalciuria as the common alteration: Dent's disease, Bartter's disease (type 1 and 2), distal tubular acidosis, primary hypomagnesemia-hypercalciuria-nephrocalcinosis syndrome. These tubular disorders are monogenic and were found in 33% of newborn with nephrocalcinosis (26). Conversely, iatrogenic causes were responsible of 30-50% of infant nephrocalcinosis (26). Furosemide and vitamin D are the most frequently implicated drugs, probably due to their capability to increase calcium excretion (27,28). Nephrocalcinosis was also associated to the use of gentamicine, extreme prematurity and severe respiratory disease (29). Vitamin D, with calcium or phosphate salts, is used to maintain normal plasma concentrations of calcium and phosphate in children with hypoparathyroidism or renal rickets, in their different forms. Because these patients are predisposed to lose calcium in urine, therapy with bivalent ions and vitamin D increases their calcium excretion to an extent that greatly amplifies the risk for renal calcium-phosphate precipitation.
Hypercalciuria was observed in 34% of newborns with nephrocalcinosis (27), but increased oxalate and urate excretions and decreased citrate excretion were also described (29). Plasma calcium concentrations, calcium and phosphate intake were found increased in newborns with nephrocalcinosis (27). Nephrocalcinosis can solve in 50% of infants, but resolution is less probable in children with hypercalciuria (30).
In adults, nephrocalcinosis usually occurs in patients with primary hyperparathyroidism or sarcoidosis or in patients chronically taking calcium or phosphate salts and vitamin D for control of hypocalcemia or hypophosphatemia. In addition, nephrocalcinosis can develop in patients with medullary sponge kidney and severe infectious or ischemical diseases of kidney.
Nephrocalcinosis can progressively damage kidney function, impairing glomerular filtration rate and urinary concentration capacity. Deterioration of renal function may be slight with time but it is correlated with the degree of nephrocalcinosis and to severity of the underlying disorder (30). Nephrolithiasis may complicate nephrocalcinosis and was reported in 4% of children (27). It may occur when an interstitial deposit erupts into urinary tract and becomes a site for salt deposition open to the urinary tract (24).
Mechanisms leading to interstitial calcium phosphate deposits are not known. Similar to nephrolithiasis, in nephrocalcinosis there may be an imbalance between inhibitors and promoters of calcium salt precipitation (26). Few models of experimental nephrocalcinosis have been tested. Anoxic incubation of rat renal cortex gave rise to calcification that began at the inner surface of cellular membranes and in mitochondria. Deposits were initially constituted by amorphous calcium-phosphate, while later by apatite (31). Npt2 knock-out rats, in which sodium-phosphate carrier (Npt2) was disrupted, developed nephrocalcinosis, due to deposition of apatite diffusely placed in renal cortex, medulla and papilla. The presence of calcifications was associated with tubular cell expression of osteopontin which may have a protective role (32).
Physical-chemical factors can be implicated in the appearance of calcification within medullary interstitium: high concentration of salts, bundle disposition of tubules and vasa recta, slow blood circulation and countercurrent mechanism may make medulla the preferential place for salt deposition.
Hypercalciuria is the alteration most frequently detected in patients with nephrocalcinosis. Due to this point, hypercalciuria has been proposed as a cause of nephrocalcinosis, but the specific role of calcium in mechanisms for tissue salt deposition remains unknown.

**Hypercalciuria and arterial hypertension**

An alteration of calcium metabolism has been hypothesized in patients with arterial hypertension and could be revealed by hypercalciuria (33). Many strains of hypertensive rats are hypercalciuric, suggesting that hypercalciuria and hypertension may share a common genetic substrate (34). High calcium excretion can be found also in hypertensive patients and the prevalence of hypercalciuria among these patients was around 35% (3, 33). To explain their association, it has been hypothesized that hypercalciuria may predispose subjects to hypertension inducing a condition of chronic calcium deficiency (35). This hypothesis was supported by studies displaying that the prevalence of hypertension was low in populations with high dietary calcium intake (36). However, the study of anti-hypertensive effect of oral calcium supplements gave controversial results in double-blind trials (37,38). Meta-analyses of these trials confirmed an hypotensive effect of calcium supplements on systolic blood pressure, but the degree of its effect was too small to propose the use of calcium as an anti-hypertensive drug. These meta-analyses also concluded that calcium anti-hypertensive activity could be exerted only in specific responsive subgroups of patients (39).
The supposed pathogenetic link between hypercalciuria and hypertension has not been yet explained. Researchers addressed their studies to the analysis of cell calcium transport in kidney or vascular cells, but these studies provided no defini-

tive results, although a reduction of calcium transport was recorded in erythrocytes and kidney tubular cells (40-41). Alternatively, hypercalciuria could be considered as an epiphenomenon, occurring in patients with volume-dependent hypertension, characterized by hypertensive response to sodium-chloride load and low plasma renin activity (42). This second possibility is today felt by the researchers as more likely in a large part of hypertensive patients.

## Conclusions

Clinical findings indicate that primary hypercalciuria predisposes affected subjects to nephrolithiasis and nephrocalcinosis, even though its specific pathogenetic role has not been elucidated in both disorders. The effect of hypercalciuria is likely to depend on unusually high calcium concentrations in urine or tubular fluid of patients. When calcium concentrations exceed the threshold for precipitation, calcium salts may be deposited in renal interstitium or tubular lumen. Salt precipitation may be easier in kidney papilla, due to its particular architecture and physical-chemical characteristics of its fluids in tubules and interstitium.

The pathogenesis of nephrocalcinosis or nephrolithiasis may be similar in hypercalciuric subjects. This possibility is indicated by the presence of both defects in patients with tubular disorders and by the presence of nephrolithiasis in heterozygous relatives of homozygous patients with hypomagnesemia-hypercalciuria-nephrocalcinosis syndrome or other tubular disorders (43). However, other factors in addition to hypercalciuria may be needed to cause the appearance of nephrocalcinosis or nephrolithiasis.

Irrespective to its causal role, the presence of hypercalciuria may be clinically relevant because it may predict individual susceptibility to stones or other disorders like arterial hypertension or osteoporosis. Epidemiological studies have to confirm the real predictive power of hypercalciuria, but in the case of positive results, the measurement of 24 hour calcium excretion should become an instrument to identify subjects susceptible to these disorders and to prevent them.

## References


1. Hodgkinson A, Pyrah LN. The urinary excretion of calcium and inorganic phosphate in 344 patients with calcium stone of renal origin. Brit J Surg. 1959;46:10-18.
2. Pak CY. Kidney stones. Lancet. 1998;351:1797-1801.
3. Moxey-Mims MM, Stapleton FB. Hypercalciuria and nephrocalcinosis in children. Curr Opin Pediatr. 1993;5:186-90.
4. Quereda C, Orte L, Sabater J, Navarro-Antolin J, Villafruela J, Ortuno J. Urinary calcium excretion in treated and untreated essential hypertension. J Am Soc Nephrol. 1996;7:1058-1065.
5. Giannini S, Nobile M, Delle Carbonare L, Lodetti MG, Vittadello G, Minicuci N, Crepaldi G. Hypercalciuria is a common and important findings in postmenopausal women with osteoporosis. Eur J Endocrinol. 2003;149:209-213.
6. Muller D, Hoenderop JGJ, Vennekens R, Eggert P, Harangi F, Mehes K, Garcia-Nieto V, Claverie-Martin F, vanOs CH, Nilius B, Bindels RJM. Epithelial Ca channel (ECAC1) in autosomal dominant idiopathic hypercalciuria. Nephrol Dial Transplant. 2002;17: 1614-1620.
7. Walser M. Calcium clearance as a function of sodium clearance. Am J Physiol 1961;200:1099-1104.
8. Hess B, Ackermann D, Essig M, Takkinen R, Jaeger P. Renal mass and serum calcitriol in male primary calcium renal stone formers: role of protein intake. J Clin Endocrinol Metab. 1995;80: 1916-1921.
9. Vezzoli G, Caumo A, Baragetti I, Zerbi S, Bellinzoni A, Centemero A, Rubinacci A, Moro GL, Adamo D, Bianchi G, Soldati L. Study of calcium metabolism in idiopathic hypercalciuria by strontium oral load test. Clin Chem. 1999;45:257-261.
10. Levy FL, Adams-Huet B, Pak CYC. Ambulatory evaluation of nephrolithiasis: an update of a 1980 protocol. Am J Med. 1995;98: 50-59.
11. Vezzoli G, Soldati L, Proverbio MC, Adamo D, Rubinacci A, Bianchi G, Mora S. Intestinal calcium absorption is associated with bone mass in stone-forming women with idiopathic hypercalciuria. Am J Kidney Dis. 2003;42:1177-1183.
12. Battaille P, Achard JM, Fournier A, Boudailliez B, Wuyteel MD, El Espe N, Bergot C, Jans I, Lalau JD, Petit J, Heron G, Laval Jeantet MA, Bouillon R, Sebert JL. Diet, vitamin D and vertebral mineral density in hypercalciuric calcium stone formers. Kidney Int. 1991;39:1193-1205.
13. Aladjem M, Modan M, Lusky A, Geiger B, Orda S, Eshkol A, Lotan D, Boichis H. Primary hypercalciuria: a familial generalized renal hyperexcretory state. Kidney Int. 1983;24:549-554.
14. Lemann J. Calcium and phosphate metabolism: an overview in health and in calcium stone formers. In: Coe FL, Favus MJ, Pak CY, Parks JH, Preminger GM, Eds. Kidney Stones, medical and surgical management. 1st Ed. Philadelphia: Lippincott-Raven Ltd; 1996:259-288.
15. Robertson WG, Heyburg PJ, Peacock HM, Hanes FA, Swaminathan R. The effect of animal protein intake on the risk of calcium stone formation in the urinary tract. Clin Sci. 1979;57:285-288.
16. Mulloy AV, FP, Freaney R, Barnes E., Dietary chloride and urinary calcium in stone disease. Q J Med. 1994;87:501-509.
17. Cirillo M, Stellato D, Panarelli P, Laurenzi M, De Santo N. Cross-sectional and prospective data on urinary calcium and urinary stone disease. Kidney Int. 2003;63:2200-2206.
18. Strauss AL, Coe FL, Deutsch L, Parks JH. Factors that predict relapse of calcium nephrolithiasis during treatment. Am J Med. 1982;72:17-24.
19. Finlayson B. Renal lithiasis in review. Urol Clin North Am. 1974;1: 181-211.
20. Knorle R, Schnierle P, Koch A et al. Tamm-Horsfall glycoprotein: role of inhibition and promotion of renal calcium oxalate stone formation studied with Fourier-transform infrared spectroscopy. Clin Chem. 1994;40:1739-1743.
21. Kok DJ, Khan SR. Calcium oxalate nephrolithiasis, a free or fixed particle disease. Kidney Int. 1994;46:847-854.
22. Khan SR. Pathogenesis of oxalate urolithiasis: lessons from experimental studies with rats. Am J Kidney Dis. 1991;17:398-401.
23. Khan SR, Finlaynson B, Hackett RL: Experimental calcium oxalate nephrolithiasis in rat. Am J Pathol. 1982;107:59-69.
24. Randall A. Papillary pathology as a precursor of primary renal calculus. J Urol. 1940;44:580-589.
25. Evan AP, Lingeman JE, Coe FL, Parks JH, Bledsoe SB, Shao Y, Sommer AJ, Paterson RE, Kuo RL, Grynpas M. Randall's plaque of patients with nephrolithiasis begins in basement membranes of thin loops of Henle. J Clin Invest. 2003;5:607- 616.
26. Schell-Feith EA, List-vanHolthe JE, Conneman N, vanZwieten PHT, Holscher HC, Zonderland HM, Brand R, van der Heijden BJ. Etiology of nephrocalcinosis in preterm neonates: association of nutritional intake and urinary parameters. Kidney Int. 2000;58: 2102-2110.
27. Ronnefarth G, Misselwitz J. Nephrocalcinosis in children: a retrospective survey. Pediatr Nephrol. 2000;14:1016-21.
28. Lin MT, Tsau YK, Tsai WY, Tsai WS, Lu FL, Hsiao PH, Chen CH. Nephrocalcinosis in childhood. Acta Paediatr Taiwan. 1999;40: 27-30.
29. Narendra A, Whiteb MP, Roltonc H A, Alloubb Z I, Wilkinsond G, McColle J H, Beattie J. Nephrocalcinosis in preterm babies. Arch Dis Child Fetal Neonatal Ed 2001;85:F207-F213.
30. Pope JC, Trusler LA, Klein AM, et al. The natural history of nephrocalcinosis in premature infants treated with loop diuretics. J Uro.l 1996;156:709-712.
31. Kim KM. Nephrocalcinosis in vitro. Scan Electron Microsc. 1983; 3:1285-92.
32. Chau H, El-Maadawy S, McKee MD, Tenenhouse HS. Renal calci-

fication in mice homozygous for the disrupted type II Na/Pi cotransporter gene Npt2. J Bone Miner Res. 2003;18:644-57.
33. Young EW, Morris CD, McCarron DA, Urinary calcium excretion in essential hypertension. J Lab Clin Med. 1992;120:624-632.
34. Bianchi G, Salvati P, Ferrari P, Vezzoli G. Renal mechanisms and calcium in the pathogenesis of a type of genetic hypertension. J Cardiovasc Pharmacol. 1986; 8 (suppl 8):s124-s129.
35. McCarron DA, Morris CD. The calcium deficiency hypothesis of hypertension. Ann Int Med. 1987;107:919-922.
36. McCarron DA, Morris CD, Henry HJ. Blood pressure and nutrient intake in the United States. Science. 1984;224:1392-1398.
37. Belizan J, Villar J, Pineda O, Gonzales AE, Sainz E, Garrera G, Sibrian R. Reduction od blood pressure with calcium supplementation in young adults. JAMA. 1983;249:1161-1165.
38. Johnson NE, Smith EL, Freudnheim JL. Effect on blood pressure of calcium supplementation of women. Am J Clin Nutr. 1985;42: 12-17.
39. Bucher HC, Cook RJ, Guyat bGH, Lang JD, Cook DJ, Hatala R, Hunt DL. Effect of dietary calcium supplementation on blood pressure. A meta-analysis of randomized controlled trials. JAMA. 1996;275:1016-1022.
40. Postnov YV, Orlov SN, Reznikova MB, Rjazhsky GG, Pokudin NI. Calmodulin distribution and Ca transport in the erythrocytes of patients with essential hypertension. Clin Sci. 1984;66:459-463.
41. Cirillo M, Galletti F, Strazzullo P, Torielli L, Melloni MC. On th pathogenetic mechanism of hypercalciuria in genetically hypertensive rats of Milan Strain. Am J Hypertens. 1989;2:741-746.
42. MacGregor GA, Cappuccio FP. The kidney and esse[illegible] hypertension: a link to osteoporosis. J Hypertens. 1993;11 781-785.
43. Weber S, Schneider L, Peters M, Misselwitz J, R[illegible]nnefart G, Boswald M, Bonzel KE, Seeman T, Sulakova T. Novel paracalcin-1 mutations in 25 families with familial hypomagnesemia with hypercalciuria and nephrocalcinosis. J Am Soc Nephrol. 2001;12:1872-1881.