Kidney complications in primary hypercalciuria

Giuseppe Vezzoli
Teresa Arcidiacono
Cristiana Bianchin
Annalisa Terranegra
Laura Soldati

Division of Nephrology Dialysis and Hypertension and Postgraduate School of Nephrology, San Raffaele Scientific Institute, Milan, Italy
* Department of Sciences and Biomedical Technologies, University of Milan, Italy

Address for correspondence:
Giuseppe Vezzoli, M.D.
Division of Nephrology, Dialysis and Hypertension
San Raffaele Scientific Institute
Via Olgettina, 60
20132 Milan, Italy
Ph. +39 02 26433006
Fax +39 02 26432384
E-mail: vezzoli.giuseppe@hsr.it

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, not all those patients with high calcium levels in urine develop kidney stones. In spite of these simple criteria, the real mechanisms 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. Despite 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.

Despite 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 is 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

A minority of patients, primary hypercalciuria results from an increase of intestinal calcium absorption (absorptive hypercalciuria) (9,10). 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 vertebral level have type levels and make hypercalciuric subjects more sensitive to stimuli inducing calcium excretion.

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.

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tuberal 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 explored the effect of factors that play a role in calcium absorption to show 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 acidic amino acids, primary to the metabolism of methionine and alanine, can increase the excretion of calcium in urine (2). A high dietary intake of animal proteins, sodium or calcium, the effect on calcium excretion should result from the combination of their influences in bones, intestine and kidney.

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Hypercalciuria and calcium stone production

Kidney stones 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, in autopsies (17). Previous studies had limited their observation to the higher frequency of hypercalciuria in calcium stone forming patients and the larger calcium excretion in re-lapsing 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 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. 1), a stone can develop from crystal agglomerates retained within the lumen of a renal tubule (21). Physical or 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 calcium in tubular lumen and exposure of basement membrane on the tubular fluid. These events may be crucial for macroaggregate development and stone formation, because crystals 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 fluids (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-
Nephrocalcinosis can solve in 50% of infants, but resolution is found increased in newborns with nephrocalcinosis (27). Calcium concentrations, calcium and phosphate intake were risk for renal calcium-phosphate precipitation. With hypoparathyroidism or renal rickets, in their different prematurity and severe respiratory disease (29). Vitamin D, are the most frequently implicated drugs, probably due to their (26). Conversely, iatrogenic causes were responsible of 30-ergic and were found in 33% of newborn with nephrocalcinosis tubular acidosis, primary hypomagnesemia-hypercalciuria. Nephrocalcinosis may occur in the course of many hereditary are cortical and composed by calcium-oxalate. Frequently composed by apatite and begins within medulla. In children and preterm newborns and deposits are more 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 hypermagnesemia-hypercalciuria-nephrocalcinosis syndrome. These tubular disorders are monogenic and were found in 33% of newborn with nephrocalcinosis. Conversely, intrinsic causes were responsible of 30-50% of infant nephrocalcinosis (28). 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 hyperparathyroidism 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 formation and intake to an extent that greatly amplifies the risk for renal calcium-phosphate precipitation. Nephrocalcinosis was observed in 34% of newborns with nephrocalcinosis (27), but increased oxalate and urate excretions and other causes as 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 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 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 pathogenic 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 nephrocalcinosis in heterozygous relatives of homozygous patients with hypomagnesemia-hypercalcemia-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 despite the absence of hypercalciuria or hypercalciuric nephrocalcinosis syndrome.

References

Kidney and hypercalciuria