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 alkali 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 were 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 in 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 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 was 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 HC over a two-year follow-up.

Renal phosphate leak HC has been treated with neutral potassium phosphate. Daily dosages of 40 mmole 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 one with encouraging results.

KEY WORDS: hypercalciuria, nephrolithiasis, thiazides, potassium citrate, bisphosphonates, pataki-amberlyte.

Introduction

Idiopathic hypercalciuria is the most frequent metabolic abnormality since up to 40 to 60% of patients with nephrolithiasis are hypercalciuric (1-5). 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 this 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.

<table>
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<tr>
<th>Diet and Fluid intake</th>
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<td>Thiazides</td>
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<td>Alkali</td>
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<td>Bisphosphonates</td>
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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 E2, which is likely involved in the pathogenesis of hypercalcemia, 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 turnover 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 hypercalcemia, but not in those with absorptive hypercalcemia, and this effect was attributed to a reduction of serum levels of calcitriol (18). Reduction of serum intestinal absorption was also observed by Coe et al. in 7 patients with severe hypercalcemia after 3 and 6 months of either chlortalidone or trichlormethiazide: despite this, calcium retention improved but fractional absorptive calcium decreased even in the absence of changes in serum calcitriol levels (19). No changes were seen in calcitriol and parathormone serum concentrations (12). Fauvs 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 urinary calcium excretion and did not alter intestinal calcium absorption (20). The issue of calcium absorption and thiazides is important to 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 often 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 thiazide use was associated with negative calcium balance and enhanced bone remodelling, in both adults (20) and children (21). The favourable effects on stone recurrence were obtained by using higher dosages, i.e. hydrochlorothiazide 50 mg twice daily (10) or chlortalidone 50 mg/day (22), were confirmed with lower doses and even in the absence of a marked reduction of calcium excretion (13,23). A potassium citrate supplement had no protective effect for the use of lower dosages is to reduce the impact of side-effects, including hypotension, potassium wasting and hypopotassiemia, increase of plasma blood pressure (serum urate), and a consequent decrease in citrate excretion. The latter event may be as important for offsetting 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 (10) or trichlormethiazide, alone or in association with amiloride (11). 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). Thus, a citrate-amiloride combination may be considered for patients who are particularly prone to calcium oxalate stone formation. This is particularly true for patients with primary hyperparathyroidism, in whom citrate supplementation is being studied (36).

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).

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, hypercalcaemia 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 urinary 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
renal tubule could be responsible for hypophosphatemia, activation of the renal 1α,25(OH)\textsubscript{2} vitamin D\textsubscript{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 hypothesized tubuloglomerular feedback defect results from a Na\textsuperscript{+}–phosphate co-transporter 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)\textsubscript{2} vitamin D, hypercalcemia, hypercalciuria and low PTH (52). Partially deficient mice [Npt2(+/-)] had similar, though milder changes. It was suggested these features are typical of patients with hereditary hypophosphatemic rickets (HHHR) and that patients with phosphate leak hypercalciuria could have heterozygous 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 calcium phosphate, was given to patients with absorptive hypercalciuria. In a short-term study daily dosages corresponding to 40 mmoles of phosphate and 83.5 mmoles of calcium decreased 24-hr and fasting urinary calcium by 40% 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 with 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 1α-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 harbour mutations leading to altered calcium excretion. The chloride channel 5 (CIC-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 hypophosphatemic hypercalciuria. The mechanism leading to hypercalciuria in Dent’s syndromes is as yet not fully elucidated, in that both intestinal hyperabsorption and renal phosphate leak could contribute. Chlorothiazide, but not amiloride, was shown to reduce both calcium excretion and calcium-salts 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 hypercalciuric response to thiazides indicates that inhibition of the CIC-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

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Table II - Genetic hypercalciuria.

<table>
<thead>
<tr>
<th>Protein</th>
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<th>Disease</th>
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<td>CLCN5</td>
<td>X-linked</td>
<td>Dent’s syndrome and related disorders</td>
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<td>Ca\textsuperscript{2+} Sensing* Receptor</td>
<td>CaR</td>
<td>Autosomal dominant</td>
<td>Familial hypocalcemic hypercalciuria (FHH)</td>
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<tr>
<td>Paracellin-1</td>
<td>PCLN-1</td>
<td>Autosomal recessive</td>
<td>Familial hypomagnesiemic hypercalciuria and nephrocalcinosis (FHHNC)</td>
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* Mutation inducing gain of function

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