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Research Article

Nephrolithiasis Associated with Normocalcemic or Hypercalcemic Primary Hyperparathyroidism: An Update on Medical Management

Abstract

Primary hyperparathyroidism (PHPT) is a disease involving a broad range of alterations of calcium homeostasis, sustained by parathyroid hormone (PTH) levels that are clearly abnormal. The anomalies directly associated with hyperparathyroidism are nephrolithiasis and fibrocystic bone disease. Since PHPT resolves when abnormal parathyroid tissue is removed, surgery is clearly the only definitive approach to this type of hyperparathyroidism. However there are large subgroups of patients for whom medical therapy should be considered instead of surgery. Pharmacological therapy consists largely of biphosphonates, or calciomimetics such as cinacalcet. Recent preliminary data suggests however that cinacalcet could also be effective in the specific group of patients with primary hyperparathyroidism associated with nephrolithiasis. Finally, since cinacalcet reduces calcemia in most PHPT patients without improving bone mass, whereas biphosphonates and especially alendronate improve bone mass, it could make sense to combine the two drugs in PHPT patients with concomitant bone loss and possibly nephrolithiasis who cannot or do not wish to undergo surgery.

Introduction

Primary hyperparathyroidism (PHPT) is a disease involving a broad range of alterations of calcium homeostasis, sustained by parathyroid hormone (PTH) levels that are elevated or at the upper limit of the normal range and therefore clearly abnormal. The alterations may vary from severe symptomatic forms of hypercalcemia (known as parathyroid crises) to forms of normocalcemic PHPT [1,2]. Indeed, in the context of any other cause of hypercalcemia, except those related to thiazide diuretics, lithium salts or the form known as familial hypocalciuric hypercalcemia (a rare autosomal dominant disorder characterised by chronic bland hypercalcemia, normal PTH levels and reduced urinary excretion of calcium), PTH levels are suppressed [1,3]. Primary hyperparathyroidism is a common endocrine disorder having a prevalence of 1-4 per 1000 persons. It occurs at any age, although it is more frequent in post-menopausal women and 85-90% of cases are caused by isolated parathyroid adenoma, or by diffuse hyperplasia of all glands; it occurs in less than 1% of cases of carcinoma [4,5]. The most common clinical manifestation of PHPT is asymptomatic, a term introduced to define patients without evident signs or symptoms that can be ascribed to an increase in calcemia and/or PTH; indeed in this form, hypercalcemia is bland (generally < 1 mg/dl above the normal range) and PTH levels are only moderately elevated (generally < 1.5-2 times the upper limit of the normal range) [6]. With time, however, some patients with the asymptomatic form of PHPT may manifest the classical form which is by definition symptomatic [2] and generally characterised by concentrations of serum calcium 1 mg/dl or more above the normal range [7]. The classical form in fact shows signs and symptoms reflecting the combined effect of elevated PTH and hypercalcemia. The anomalies directly associated with hyperparathyroidism are nephrolithiasis and fibrocystic bone disease, while symptoms attributed to hypercalcemia include anorexia, nausea, constipation, polydypsia and polyuria [2].

Nephrolithiasis also occurs in the most recently discovered form of hyperparathyroidism, namely the normocalcemic form. This specific phenotype of PHPT, in which levels of PTH are elevated but calcemia is normal, was only recognised internationally in 2009 [8]. For a correct diagnosis, it is necessary to exclude all possible secondary causes of hyperparathyroidism, such as 25-OH vitamin D deficiency, reduced creatinine clearance, use of drugs such as hydrochlorothiazide and lithium salts, idiopathic hypercalciuria and gastrointestinal disorders linked to malabsorption syndromes [9], as well as to ascertain that total and ionised calcemia are normal. To sustain diagnosis it is essential to exclude concomitant vitamin D deficiency, which is often the cause of elevated PTH levels [1]. Normocalcemic PHPT was considered an initial form of PHPT in which elevated PTH levels preceded the manifestation of clear hypercalcemic values, however in an observational study on 37 patients with this specific form of PHPT, less than 20% of patients became hypercalcemic during the observation period and some persistently normocalcemic patients developed renal calculi, hypercalciuria, bone loss and fractures [10]. In any case, nephrolithiasis, the aspect that concerns us here, is the most common complication of PHPT, occurring in 15-20% of patients with the hypercalcemic form [11] and even the normocalcemic form seems burdened with a similar high prevalence of nephrolithiasis (18.2% according to Amaral et al.) [12]. Subclinical nephrolithiasis has also been described in patients with the asymptomatic form, and indeed subclinical nephrocalcinosis and nephrolithiasis are

more common in patients with than without hyperparathyroidism [13], as demonstrated by a review of 271 renal ultrasonograms from patients with asymptomatic PHPT, confirmed surgically, in whom the prevalence of renal calculi found by ultrasound performed 6 months before parathyroidectomy proved significantly higher than in age-matched subjects undergoing renal ultrasonography for other reasons [14].

Calcium oxalate is the constituent of most kidney stones found in patients with PHPT except in case of slightly alkaline urine when calcium phosphate becomes the constituent of such kidney stones [15]. In this context, hypercalciuria (caused by the fact that an increase in the amount of filtered calcium linked with hypercalcemia more than compensates distal tubular reabsorption of calcium directly induced by PTH) is a predisposing factor for the formation of such calculi [16] and determines an increase in urinary excretion of calcium in 35-40% of patients with PHPT. Nevertheless, PHPT patients with nephrolithiasis cannot be differentiated from those without on the basis of urinary excretion of calcium per gram of creatinine [17]. Indeed, research aimed at comparing biochemical profiles of hyperparathyroidism patients with and without associated nephrolithiasis [17,18] found hypercalciuria in only 39% of all hyperparathyroidism patients examined and only 29% of those with hypercalciuria had associated nephrolithiasis [2]. It is therefore unclear why certain PHPT patients, whether normo or hypercalcemic, develop nephrolithiasis while others do not, although it seems likely that the causes could lie in the complexity of factors determining the formation of renal calculi. Urinary excretion of calcium is indeed only one of at least six urinary risk factors influencing urinary supersaturation with calcium salts that leads to calculus formation. Besides hypercalciuria, factors that could contribute to the formation of calcium oxalate stones in PHPT include hyperoxaluria, hypocitraturia, dietary risk factors such as low calcium intake, high oxalate intake, high animal protein intake (that may increase urinary excretion of uric acid and lower urinary pH, reducing urinary excretion of citrates), high salt intake, low liquid intake and high serum concentrations of calcitriol (caused by renal hydroxylation of 25-OH vitamin D by PTH, which may contribute to hypercalciuria and formation of renal calculi) [1,16,18,19].

We therefore do not know what predisposes PHPT patients to kidney stone formation [1], but since serum concentrations of calcium are genetically controlled in normal individuals [20,21] and are maintained in a narrow range by PTH, the action of which is mediated by calcium-sensing receptors (CaSR) expressed on parathyroid glands and renal tubule cells, it is possible that a specific role in the genesis of forms of PHPT associated with nephrolithiasis is played by polymorphism of three nucleotides in exon 7 of the CaSR gene [22]. These nucleotides prove to be predictors of serum concentrations of calcium in the normal Caucasian population, both individually and in haplotype combination [23-25] as confirmed by the clinical study of Scillitani et al. [26], which demonstrated that PHPT patients carrying the AGQ haplotype are at greater risk for renal calculi.

Clinical management of nephrolithiasis associated with primary hypercalcemic or normocalcemic hyperparathyroidism

Since PHPT resolves when abnormal parathyroid tissue is removed, surgery is clearly the only definitive approach to this type of hyperparathyroidism [1]. Patients with symptomatic PHPT (especially those with nephrolithiasis and symptomatic hypercalcemia) should therefore undergo parathyroid surgery, the only definitive therapy. Parathyroidectomy is indeed an effective therapy that reduces the risk of nephrolithiasis, improves bone mass and may reduce the risk of fractures. Observational studies report a sharp reduction in renal calculus formation after effective parathyroidectomy [27,28] and in the course of 10 years of clinical monitoring, all patients with a history of nephrolithiasis who did not undergo parathyroidectomy suffered progression of the disease [28]. This is why a medical history of nephrolithiasis in the context of PHPT is considered a clear indication for surgery. In the case of asymptomatic PHPT, it is necessary to distinguish between patients who do not have progressive disease (defined by precipitation of hypercalcemia, hypercalciuria, bone disease and/or nephrolithiasis) and for whom surgery is therefore not mandatory, and patients who suffer progression towards a clinical aspect of the symptomatic form and who can therefore be helped by surgery [29]. Criteria to identify subjects with the symptomatic form of PHPT, who could be candidates for surgery, include demonstration of nephrolithiasis or nephrocalcinosis by traditional imaging methods (ultrasonography, radiography or CT) [7].

Finally, for patients with the normocalcemic form of PHPT, there is insufficient data to define specific therapeutic guidelines, though in clinical practice symptomatic patients (i.e. with nephrolithiasis or evident skeletal involvement) should undergo therapy as recommended for patients with the classical symptomatic form of PHPT. On the other hand, patients with an asymptomatic form of normocalcemic PHPT may in any case develop symptoms and they therefore should be constantly monitored for progression, which could lead to an indication for surgery [7]. Where surgery is not recommended, it is nevertheless appropriate to implement preventive support and adequate monitoring, including at least yearly determination of calcemia and creatininemia, and two-yearly checks to exclude changes in bone density; the possibility of nephrocalcinosis or a silent form of nephrolithiasis should also be excluded by renal ultrasonography or other imaging method, at least at the initial diagnosis [7].

Among possible preventive measures, it is advisable to avoid factors that could aggravate hypercalcemia, such as thiazide diuretics, lithium salts, prolonged immobilisation or inactivity. Physical activity can help to minimise bone resorption, while fluid intake should be increased to reduce the risk of kidney stone formation, at the same time maintaining moderate calcium intake (1000 mg/day). A low calcium diet can promote the production of PTH and aggravate associated bone disease [7,30], except in patients with high serum calcitriol concentrations, for whom 1000 mg/day calcium is known to exacerbate hypercalcemia and hypercalciuria, and in whom calcium intake should therefore be reduced (<800 mg/day) [8,31].

However there are large subgroups of patients for whom medical therapy should be considered instead of surgery:

1. patients meeting the criteria for surgery but who are ineligible for other reasons, or refuse it;

2. patients with PHPT refractory to parathyroidectomy;
3. asymptomatic patients unwilling to undergo surgery, despite the benefits it would bring [7,32].

Pharmacological therapy consists largely of biphosphonates that inhibit bone resorption and may increase bone density while lowering blood and urinary concentrations of calcium, or calciomimetics such as cinacalcet, that act as activators of calcium-sensing receptors at parathyroid and renal level, thus suppressing parathyroid secretion and reducing calcemia while increasing phosphoremia [7].

Biphosphonates are potent inhibitors of bone resorption and may be useful to recover bone mass in PHPT patients not undergoing parathyroidectomy, as shown by a small number of studies in which alendronate was administered for one or two years to patients with bland PHPT. An increase in femoral and spinal but not radial bone density was recorded. In at least two of these studies, transient increases in PTH and small decreases in calcemia and urinary excretion of calcium were observed in the first month of therapy, followed by a return to initial values in the subsequent two years of observation [33-36]. In a brief observation period of two years, biphosphonates equalled increases in bone mass recorded after parathyroidectomy. Primary hyperparathyroidism is however a chronic diseases and concern has been expressed about the long-term side-effects of biphosphonates [7]. Reductions in serum levels of calcium are detected by calcium-sensing receptors on parathyroid glands, leading to an increase in synthesis and secretion of PTH, which in turn stimulates bone resorption mediated by osteoclasts and increases synthesis of 1,25-dihydroxy vitamin D in the proximal renal tubules. This in turn leads to an increase in intestinal absorption of calcium and phosphorus, as well as mobilisation of skeletal calcium, which normalises calcemia and induces release of fibroblast growth factor 23 that increases renal losses of phosphorus, reduces PTH secretion and inhibits hydroxylation of 25-OH vitamin D, thus closing the feedback that regulates homeostasis of serum calcium. On the other hand, any rise in serum levels of calcium leads to a decrease in the synthesis and secretion of PTH (by calcium binding to CaSR on the parathyroid glands), to an increase in renal loss of calcium (also by the direct effect of calcium on CaSR in the distal renal tubules) and to reduction in 1,25-hydroxy vitamin D and hence to reduction in calcium release from bone. Thus the final result is normalisation of serum calcium concentrations [4,5].

We observe that calciomimetic agents such as cinacalcet hydrochloride function as activators of calcium-sensing receptors at parathyroid and renal level, thus suppressing secretion and synthesis of PTH, with consequent reduction in calcemia and elevation/reduction of phosphoremia, depending on whether or not the kidneys are functional [37-39].

Cinacalcet, the only available calcium mimetic agent, may be used to treat secondary hyperparathyroidism in patients with kidney failure or hypercalcemia due to parathyroid cancer, and in severe forms of hypercalcemia in PHPT patients ineligible for parathyroidectomy. Indeed, cinacalcet reduces calcemia in most PHPT patients, as shown for example by a one-year study in which 78 PHPT patients were assigned cinacalcet or placebo. Cinacalcet normalised calcemia in 73% of patients and PTH concentrations dropped by 7.5%, but bone density did not change and there was no significant change in 24-h urinary excretion of calcium [40]. The same results (reduction in blood levels of PTH and normalisation of calcemia without changes in bone density) were confirmed by monitoring the patients over a longer interval [41]. Thus cinacalcet may be used to normalise calcemia in symptomatic hypercalcemia patients who cannot or do not wish to undergo parathyroidectomy, especially when bone density is normal, since the drug does not reduce bone turnover or increase bone density. In any case, since the technical success of surgery is less than 100% and varies widely between centres (without considering the risk of general anaesthesia which may be higher in developing countries), medical therapy with cinacalcet may be viewed as a valid alternative to surgery in patients with persistent hypercalcemia after one or more surgical operations [32,42]. With regard to the effects of cinacalcet on calciuria, we observe in more detail that Peacock et al. [40], recorded a reduction of calciuria in first morning urine samples, as well as in 24-h urine samples, but the reduction was statistically significant only in the former. This pattern presumably depends on the complexity of the mechanism of action of cinacalcet, which on one hand determines an increase in calciuria at renal level (by activation of CaSR in the renal tubules) and on the other balances this effect with a concomitant reduction in PTH levels and hence in calcemia. This reduces the amount of calcium filtered, as demonstrated by Crockett et al. who reported that cinacalcet reduces PTH levels, normalising calcemia, without increasing urinary excretion of calcium [32,43]. The fact that the reduction in calciuria of the first morning sample was not reflected in 24-h samples could be due to the fact that calciuria in the latter reflects a component related to intestinal absorption of calcium, which seems elevated in hyperparathyroid patients susceptible to formation of kidney stones [44].

Other possible pharmacological approaches to PHPT include hormone replacement therapy (estrogen/progestogen), which while reducing bone resorption in post-menopausal women with PHPT involves increased risk of breast cancer, stroke and coronary disease, and raloxifene, a selective modulator of estrogen receptors, for which there is an absence of consistent data on its use in PHPT patients [7]. Since such patients have a high prevalence of vitamin D deficiency (due to elevated PTH activity which increases renal conversion of 25-OH vitamin D to 1,25-dihydroxy vitamin D) [5], 25-OH vitamin D should be measured in all PHPT patients and supplemented in the case of deficiency (≤20 ng/ml or 50 nmol/l) [45,46]. Vitamin D deficiency may in fact be associated with higher PTH activity after parathyroidectomy and higher risk of hungry bone syndrome after surgery [47,48]. However, vitamin D supplementation may worsen hypercalcemia and hypercalciuria [49] and irrespective of the dose of vitamin D administered, special attention should be paid to patients with vitamin D deficiency and urinary excretion of calcium in the upper part of the normal range or clearly elevated, since once these individuals reach adequate vitamin D levels, their urinary levels of calcium may rise sharply, increasing the risk of kidney stones [7]. Summing up, in line with the recommendations of the Fourth International Workshop on Asymptomatic PHPT, we observe that pharmacological therapy of PHPT may be based on specific associated clinical findings, electively administering

cinacalcet to patients whose primary indication for surgery is severe or symptomatic hypercalcemia, especially when bone mass is normal [50, 40]. On the other hand, for patients whose primary indication for surgery is osteoporosis and risk of fractures, biphosphonates appear to be the elective therapy. In cases where bone density does not need to be improved or calcemia reduced, pharmacological treatment may be unnecessary. In such cases support and prevention are more appropriate, are also indicated in patients to be treated with the above drugs [7,45,51].

Recent evidence regarding use of cinacalcet in forms of nephrolithiasis associated with PHPT

Brardi et al. [52], treated ten PHPT patients with active nephrolithiasis, randomly but not blindly, with potassium citrate and allopurinol with or without cinacalcet. The dose of cinacalcet was personalised to normalise PTH while maintaining sufficient calcemia. All patients followed a low sodium, normal calcium, low protein and low oxalate diet with increased hydration. After a first 10-month observation period, therapy was varied for a second 10-month period by suspending cinacalcet to patients who were taking it and adding cinacalcet to the treatment of patients who were on potassium citrate and allopurinol alone. At the end of the observation period with cinacalcet, patients with both forms of hyperparathyroidism showed a statistically significant reduction in the overall number of stones and of the diameter of larger stones with respect to the same measures on enrolment and with respect to the period without cinacalcet. As expected, these reductions in the number and dimensions of kidney stones obtained with cinacalcet therapy were associated with variations in the endocrine and metabolic profiles of reference, namely a statistically significant reduction in calcemia and PTH and a significant increase in phosphoremia (PTH inhibits resorption of phosphorus by renal tubules and therefore increases its urinary excretion) and in first morning urine pH (elevated PTH levels cause initial transient renal acidosis, promptly balanced by an increase in net acid excretion and by release of alkaline bases arising from bone resorption), without any significant variations in calciuria [32,53].

No significant variations in calciuria were expected from cinacalcet treatment because, as already mentioned, activation of calcium-sensing receptors in renal tubules, induced by calcium mimetic therapy, leads to a reduction in reabsorption of calcium and therefore to an increase in calciuria, which is however balanced in most patients by simultaneous decrease in PTH and serum levels of calcium induced by the same calcium mimetic therapy [32]. Increased risk of nephrolithiasis during calcium mimetic therapy should only occur in carriers of the Arg990Gly polymorphism of calcium-sensing receptors, which leads to a permanent increase in receptor sensitivity, the reason why these patients respond more strongly to cinacalcet [32,40,43].

So the results of Brardi et al. [52], clearly show that cinacalcet, administered in association with a normal calcium diet, induced a reduction in the number and size of kidney stones solely by bringing PTH within normal limits.

More specifically, in the same study [52], cinacalcet was not used at the standard dose of 30 mg twice a day [7], but at a mean daily dose of 48.86 ± 30.09 mg, titred in each patient to bring PTH values within the normal range and to maintain calcemia within the normal range, and obviously a higher dosage (divided in two daily doses) in subjects with the hypercalcemic form of PHPT.

Indirect confirmation of the need to use cinacalcet at doses sufficient to normalise PTH and calcemia came from a case report in the literature, in which a patient with secondary hyperparathyroidism who had already undergone renal transplant developed kidney stones during cinacalcet treatment [54]. Reported by Seager et al., the case lacked full correction of PTH and calcemia by cinacalcet. The authors report persistently elevated levels of PTH (211 pg/ml) and calcemia (11.4 mg/dl) despite administration of the drug and there is evidence that when cinacalcet was suspended, PTH levels and calcemia were substantially unchanged with respect to before therapy, and indeed calcemia increased.

Cinacalcet, associated with a normal calcium diet, administered at doses sufficient to normalise PTH and calcemia, could therefore be an option for treating patients with nephrolithiasis associated with PHPT, whether hypercalcemic or normocalcemic (with the sole exception of carriers of the Arg990Gly polymorphism), who cannot or do not wish to undergo surgical treatment, or who have a form of hyperparathyroidism refractory to surgery.

If the nephrolithiasis is associated with a bone loss it could make sense to associate with cinacalcet that does not lead to an improvement in bone density [7], biphosphonates and especially alendronate that improve bone mass, reducing urinary excretion of calcium to a limited degree, therefore with a favourable effect on nephrolithiasis [55]. And as a proof of the validity of this option we can cite the fact that have already been published a few observational studies in which treatment with both drugs improved bone density and reduced calcemia [7,45,56,57].

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