

Use of cinacalcet in nephrolithiasis associated with normocalcemic or hypercalcemic primary hyperparathyroidism: Results of a prospective randomized pilot study

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Summary *Objectives: To evaluate, by means of a prospective randomized study, the efficacy of cinacalcet in the forms of nephrolithiasis associated with primary hyperparathyroidism in both the hypercalcemic and normocalcemic variant.*

Materials and Methods: Ten patients suffering from active nephrolithiasis associated with primary hyperparathyroidism (4 hypercalcemics and 6 normocalcemics), equally divided between males and females, were randomly but not blindly addressed to treatment with potassium citrate and allopurinol, or to the same therapeutic regimen in combination with cinacalcet. The dosage of cinacalcet was optimized for each patient in order to obtain a reduction of parathyroid hormone (PTH) within normal limits while enabling the maintenance of adequate calcemic values. All study participants were given the same diet based on a reduction in sodium intake, oxalate-rich foods and animal protein with standardized intake of calcium and an increase in hydration. After a follow up period of 10 months, cinacalcet was associated to standard therapy and diet in patients who were not taken it, conversely cinacalcet was withdrawn in the remaining patients who remained on standard therapeutic regimen and diet. Follow up was continued for a second period of observation of the same duration of the first.

Results: At the end of the period of treatment with cinacalcet, for both variants of hyperparathyroidism, a statistically significant reduction in the overall number and in the diameter of renal stones was found.

Conclusions: This prospective randomized study shows the effectiveness of cinacalcet used in combination with a diet with normalized calcium intake, in reducing the number and size of urinary stones in hypercalcemic and normocalcemic forms of primary hyperparathyroidism.

KEY WORDS: Nephrolithiasis; Normocalcemic primary hyperparathyroidism; Cinacalcet; Prospective randomized study.

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INTRODUCTION

Primary hyperparathyroidism is a disease characterized by elevated levels of *parathyroid hormone* (PTH) that in 70-80% of cases is caused by isolated parathyroid adenoma and in the remaining from a diffuse hyperplasia of all glands (1). Primary hyperparathyroidism is one of the most common endocrine disorders and classically presents with hypercalcemia, nephrolithiasis and reduced bone mass (2). Since last decade it has also been described a new clinical form of primary HPT, defined normocalcemic primary hyperparathyroidism, characterized by total and ionized calcium concentrations within the normal limits even in the presence of a constant elevation of the levels of PTH and in the absence of alterations that may justify a secondary elevation of PTH (3). Diagnosis of primary hyperparathyroidism implies absence of secondary causes of elevation of PTH such as 25-hydroxyvitamin D deficiency, decreased creatinine clearance, use of drugs such as hydrochlorothiazide and lithium salts, idiopathic hypercalciuria, gastrointestinal disorders associated with malabsorption syndromes (3). Nephrolithiasis is present in 15-20% of patients with hypercalcemic primary hyperparathyroidism (4) but also normocalcemic primary hyperparathyroidism is associated with such an high prevalence of nephrolithiasis (18.2% according to *Amaral et al.*) (2). Similar incidences were demonstrated for bone fractures (2). Most stones found in patients with primary hyperparathyroidism are composed of calcium oxalate and, in case of alkaline urine, of calcium phosphate (5). In this context, hypercalciuria (due to the fact that the increase of filtered calcium related to hypercalcemia compensates and even surpasses distal tubular reabsorption of calcium directly induced by parathyroid hormone) is a predisposing factor for stone formation (6). However it is not clear why some patients with primary hyperparathyroidism, both normocalcemic or hypercalcemic, tend to form stones and others do not. In fact, in studies that aimed at comparing the biochemical profile of patients with hyperparathyroidism with or without associated

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nephrolithiasis (7, 8) hypercalciuria was found in only 39% of the patients with hyperparathyroidism and only 29% of those with hypercalciuria had nephrolithiasis (9). On the other hand, the urinary excretion of calcium not necessarily differentiates patients with and without kidney stones because urinary excretion of calcium is only one of at least six factors that can cause urinary supersaturation of calcium salts leading to the formation of kidney stones. For this reason very high levels of urinary calcium excretion are no longer considered an indication for parathyroidectomy (9, 10). Regarding the clinical management of the two forms of primary hyperparathyroidism while there are clear indications about the hypercalcemic classical form, where a relapsing form of nephrolithiasis is considered a clear indication to parathyroidectomy (10, 11), for the normocalcemic form there are currently insufficient data to recommend parathyroidectomy or just observation (12). On the other hand, also in some classical form of hypercalcemic hyperparathyroidism, when parathyroidectomy has not a sure indication or is not feasible or is refused by the patient, there is an option for adequate monitoring and prevention measures such as hydration and a dietary regimen with normalized calcium intake similarly to that recommended in the general population or for the use of specific drugs (1). Pharmacological therapy consists mainly of bisphosphonates, which inhibit bone resorption and can increase bone density while lowering the blood concentration and urinary excretion of calcium (1) and calcimimetics, such as *cinacalcet*, which act as activators of the calcium-sensing receptor at level of both the parathyroid and the kidney and are capable of inducing a suppression of parathyroid secretion and thus reducing serum calcium levels, while increasing serum phosphorus (1, 13). *Cinacalcet* can be used to normalize the serum calcium in patients with symptomatic hypercalcemia that they cannot be submitted to parathyroidectomy, particularly if bone density is normal, because this drug is not able to reduce the bone turn-over or to increase bone mineral density (13, 14). However, effects of *cinacalcet* on calciuria are not well known and in fact in a study of *Peacock et al.* (14) urinary calcium was reduced in treated patients both in the first morning urine and in 24 hour urine, but this difference appeared statistically significant only for first morning urine. It is likely that the basis of such behavior is the complexity of the mechanism of action of *cinacalcet* that on one hand determines an increase in of calcium excretion but on the other hand reduces the levels of serum calcium and the filtered load of calcium (1). The finding of reduced urinary calcium in the early morning urine in absence of a reduction of calcium excretion in the 24-hour urine may be explained by the fact that the 24-hour urinary calcium reflects a component linked to intestinal absorption of calcium that appears to be increased in patients with hyperparathyroidism forming stones (15). To date, however, there is no data in the literature on what may be the consequence (in terms of change in the number and size of stones) arising from the use of *cinacalcet* in the forms of nephrolithiasis associated with both hypercalcemic and normocalcemic primary hyperparathyroidism (1, 11) The present pilot study was therefore intended to investigate possible direct effects on renal stone formation with the use of *cinacalcet*

in the forms of nephrolithiasis associated with both hypercalcemic and normocalcemic primary hyperparathyroidism.

MATERIALS AND METHODS

Study design

To evaluate the therapeutic effects of *cinacalcet* in patients with active nephrolithiasis associated with primary hyperparathyroidism were enrolled 10 patients equally divided between males (mean age 55.6 ± 8.3 years) and females (mean age 62.4 ± 11.8 years, all postmenopausal except one). Four patients, equally divided between males and females, were affected by the hypercalcemic variant of primary hyperparathyroidism and the other six, which are also equally divided between males and females, were instead affected by the normocalcemic variant of hyperparathyroidism (Table 1).

Criteria for inclusion and exclusion

Patients were considered eligible for the study if they had a documented active form of kidney stone disease (2 or more stones formed during the previous two years) associated to both hypercalcemic or normocalcemic primary hyperparathyroidism characterized by intact PTH levels, as determined by the method Immunoassay, consistently high (> 79.6 pg/ml). We excluded patients with known causes of secondary elevation of parathyroid hormone such as 25-hydroxyvitamin D deficiency (defined as serum 25-hydroxyvitamin D less than 20 ng/ml) (16), decreased creatinine clearance (defined as the finding of a GFR less than 50 ml/min) (14), use of drugs such as hydrochlorothiazide and lithium salts, gastrointestinal disorders associated to malabsorption of calcium and idiopathic hypercalciuria (defined as the presence of urinary calcium > 300 mg/24 h in men and 250 mg/24 h in women or urinary calcium levels in 24 hour urine greater than 4 mg/kg body weight for both sexes in the absence of known causes of hypercalciuria such as sarcoidosis, rapidly progressive osteoporosis, excessive intake of vitamin D or calcium, immobilization, hyperthyroidism, renal tubular acidosis and the presence of any neoplasm) (17). In this regard, we specify that in the study were also enrolled two patients (one male suffering from the hypercalcemic variant of hyperparathyroidism and a female affected by the normocalcemic variant hyperparathyroidism) with higher values of urinary calcium (> 4 mg/kg body weight). In order to exclude an elevation of PTH secondary to hypercalciuria, before starting the study, we treated these patients for three months with a thiazide diuretic such as hydrochlorothiazide at a dose of 12.5 mg bis in die, according to *Coe et al.* (17), and we were able to observe that despite the reduction of urinary calcium within normal limits, there was no decrease of parathyroid hormone that was further increased in association with an increase of serum calcium. On this basis we assumed that in such patients, as well as in at least another case already described in the study of *Coe et al.* (17), hypercalciuria was not the cause of the elevation of PTH that was rather primitive and independent of the levels of calciuria since it remained unchanged in spite of the correction of hypercalciuria. Such patients after

a wash out period without thiazide were then enrolled in the study. Finally, the normocalcemic forms were defined by the presence of values of total serum calcium (corrected for albumin) within normal limits with respect to the laboratory reference range used (8.4 to 10.6 mg/dl) and hypercalcemic forms were defined after at least two consecutive determinations consistently high (18).

Study protocol

Written informed consent was required to all patients at the time of enrollment. At baseline, all patients maintained their usual meals and were subjected to a screening laboratory including the blood determination of urea nitrogen, creatinine, sodium, potassium, calcium, phosphorus, uric acid, total protein, protein electrophoresis, 25 hydroxy vitamin D and parathyroid hormone while in the 24-hour urine were measured creatinine, citrate, uric acid, calcium, phosphate, oxalate and magnesium, calcium/creatinine ratio and volume. In first morning urine was measured pH and were performed urine culture and Brand test to exclude infectious forms or cystinuria. Glomerular filtration rate was then calculated with CKD EPI formula (19). Renal ultrasound was performed to evaluate presence, number and larger diameters of stones and to exclude hydronephrosis. Each patient was also subjected to medical examination with determination of weight, height and arterial blood pressure. The same blood and urine tests (except for the test of Brand) and ultrasound examination of the urinary tract were repeated at the end of each of the successive periods of observation, when the patients were again subjected to medical examination with recording of weight, blood pressure and data related to compliance with therapy and diet and any adverse reaction to the treatment. Since this was a case control study in which patients were controls of themselves, the subjects enrolled were directed to a first observation period of 10 months, during which were assigned to standard treatment with potassium citrate at a dose of 50 mEq daily and/or allopurinol at a dose of 300 mg daily, when required by alterations emerged from the metabolic study. This regimen was associated at random but not blindly to *cinacalcet* administration. The dosage of *cinacalcet* was optimized for each individual patient to obtain a reduction of PTH within normal limits while enabling the maintenance of adequate values of calcemia. At the end of the first observation period, *cinacalcet* therapy was added, for a second period of observation of the same length as the first, in patients who were not taking it, or withdrawn in patients who were assuming it in the first period. Finally, in all patients, at the time of the basal visit was prescribed an equal dietary regimen based on a reduction of sodium intake, foods rich in oxalate and protein of animal origin, with normalized intake of calcium (0, 8-1 g daily) and increase in hydration (> 2 liters daily) by use of mineral waters with moderate calcium content (20). This dietary regimen is ideal for the prevention and the contrast of nephrolithiasis even when it is associated to a form of primary hyperparathyroidism. On the contrary low calcium diet was avoided because it exposes the patient to the risk of osteopenia and has an adverse effect on the risk of stone formation because of the increase of oxalate excretion due to increased intestinal absorption of calcium (1). The parameters used to evaluate

the efficacy of therapeutic regimens and dietary regimen during each of the two observation periods were the differential variations of the above mentioned blood and urinary parameters as well as differential changes in the overall number of urinary calculi and the larger diameter of the stones. To accurately quantify the differential changes in the number of stones, spontaneous stone passages were also recorded, as evidence of the formation of new stones, in the absence of the detection of stones at the time of the entry in the study, as well as stone passages without changes in the total number of stones at the final ultrasound examination and also episodes of stone treatment with shock wave lithotripsy and/or surgical removal of stones during the follow-up period.

Data collection and statistical analysis

All determinations were carried out at the Laboratory of Analysis of the S. Donato Hospital of Arezzo using Siemens kit for citraturia, uricosuria and oxaluria based on enzymatic methods and Siemens kit for urinary calcium, phosphaturia and magnesuria based on colorimetric methods. Determination of intact parathyroid hormone was instead performed by enzyme immunoassay (*Tosoh AIA 900*). Descriptive statistics (means and standard deviation) for overall patients and group of patients were obtained. Statistical comparisons for any significant difference between sexes, observation periods and subgroups with hypercalcemic and normocalcemic variant of hyperparathyroidism were performed. Data distributions were normal to the Kolmogorov-Smirnov test and Student t test was used for significant differences between the means of samples. The parametric t test has high power and is therefore able to reveal significant differences also with reduced samples, such as those of the study in question. For multiple paired comparisons the Bonferroni correction was applied to at the level of statistical significance equal to 95% ($p < 0.05$).

RESULTS

All patients completed the two scheduled observation periods, no one was excluded because of intolerance or lack of compliance and during both observation periods no spontaneous expulsion of stones or fragments was recorded nor was necessary to practice any lithotripsy treatment and/or surgical procedure for removal of urinary calculi.

Effect of *cinacalcet* and other therapies and dietary recommendations on stone formation

At the end of the observation period with *cinacalcet* a statistically significant reduction in the total number of stones in comparison with the total number at the end of the observation period without *cinacalcet* (number of stones at the end of the observation period without *cinacalcet* 3.2 ± 2.5 versus number of stones at the end of the period of observation with *cinacalcet* 2.3 ± 2.8 ; $p = 0.019$) and with the total number at enrollment (number of stones at enrollment: 3 ± 2.5 units vs. number of stones at the end of the observation period with *cinacalcet* 2.3 ± 2.8 units; $p = 0.045$) was found, while there was no change between this figure at enrollment and the one recorded at the end of the observation peri-

od without *cinacalcet*. At the end of the observation period with *cinacalcet* it was also found a statistically significant reduction of the larger diameter of stone in comparison with the period of observation without *cinacalcet* (diameter of larger stone at the end of observation period without *cinacalcet*: 0.78 ± 0.36 cm versus larger diameter of stone at the end of the observation period with *cinacalcet*: 0.47 ± 0.38 cm; $p = 0.000$) and at enrollment (larger diameter of stone at enrollment: 0.805 ± 0.21 cm versus larger diameter of stone at the end of the observation period with *cinacalcet*: 0.47 ± 0.38 cm; $p = 0.002$), while there was no change between this figure at enrollment and the one recorded at the end of the observation period without *cinacalcet* (Table 2).

Effect of cinacalcet and other therapies and dietary recommendations on biochemical parameters

At the same time, as expected, a statistically significant reduction in serum calcium and parathyroid hormone was recorded at the end of the observation period with *cinacalcet* in comparison with both the observation period without *cinacalcet* (serum calcium at the end of the observation period without *cinacalcet* 10.2 ± 0.94 mg/dl versus serum calcium at the end of the period observation with *cinacalcet*: 8.9 ± 0.6 mg/dl; $p = 0.000$) (PTH at the end of the period of observation without *cinacalcet*: 126.5 ± 73.3 pg/ml versus PTH at the end of the period of observation with *cinacalcet*: 68.9 ± 38.7 pg/ml; $p = 0.039$) and at enrollment (serum calcium at enrollment: 10 ± 0.8 mg/dl versus serum calcium at the end of the observation period with *cinacalcet*: 8.9 ± 0.6 mg/dl; $p = 0.000$) (PTH at enrollment: 136.3 ± 72.5 pg/ml versus PTH at the end of the observation period with *cinacalcet*: 68.9 ± 38.7 pg/ml; $p = 0.016$), while there was no variation between data at enrollment and data recorded at the end of the observation period without *cinacalcet*. A statistically significant increase of serum phosphorus and first morning urinary pH was observed when data at enrollment and data recorded at the end of the observation period with *cinacalcet* were compared (serum phosphorus at enrollment: 2.9 ± 0.69 mg/dl versus phosphorus at the end of the observation period with *cinacalcet*: 3.6 ± 0.6 mg/dl; $p = 0.001$), (fasting urine pH at enrollment: 5.3 ± 0.47 versus fasting urine pH at the end of the observation period with *cinacalcet*: 6.5 ± 0.9 ; $p = 0.039$), whereas no change was found in the comparison between data found at the end of the observation period without *cinacalcet* and data at the end of the observation period with *cinacalcet* and in the comparison of data at enrollment and data at the end of the period without *cinacalcet*.

Finally a statistically significant reduction of uric acid excretion was found comparing data at enrollment and data observed at the end of the observation periods with and without *cinacalcet* (24-h urinary uric acid at enrollment: 509.1 ± 165.4 mg/24 h versus 24-h urinary uric acid at the end of the observation period without *cinacalcet*: 347 ± 118 mg/24 h; $p = 0.024$) (24-h urinary uric acid at enrollment: 509.1 ± 165.4 mg/24 h versus 24-h urinary uric acid at the end of the observation period with *cinacalcet*: $323 \pm 141 \pm 6$ mg/24 h; $p = 0.031$) whereas there was no change between the data found at the end of the two observation periods (Table 2).

Comparison of hypercalcemic and normocalcemic hyperparathyroidism

As expected, higher mean values of serum calcium (serum calcium at enrollment: 11 ± 0.16 mg/dl for the hypercalcemic variant versus 9.3 ± 0.35 mg/dl for the normocalcemic variant, $p = 0.000$; serum calcium at the end of the observation period without *cinacalcet*: 11.2 ± 0.25 mg/dl for the hypercalcemic variant versus 9.5 ± 0.24 mg/dl for the normocalcemic variant, $p = 0.000$; serum calcium at the end of the observation period with *cinacalcet*: 9.52 ± 0.35 mg/dl for the hypercalcemic variant versus 8.64 ± 0.50 mg/dl for the normocalcemic variant, $p = 0.017$) and lower mean values of serum phosphate (serum phosphate at enrollment: 2.23 ± 0.30 mg/dl for the hypercalcemic variant versus 3.4 ± 0.40 mg/dl for the normocalcemic variant, $p = 0.005$; serum phosphate at the end of the observation period without *cinacalcet* 2.4 ± 0.50 mg/dl for the hypercalcemic variant versus 3.6 ± 0.49 mg/dl for the normocalcemic variant, $p = 0.010$; serum phosphate at the end of the observation period with *cinacalcet* 3.1 ± 0.20 mg/dl for the hypercalcemic variant versus 3.97 ± 0.59 mg/dl for the normocalcemic variant, $p = 0.025$) were observed in patients suffering from hypercalcemic variant of hyperparathyroidism than in those affected by the normocalcemic variant both at enrollment and at the end of the observation period with and without *cinacalcet*.

Similarly higher mean PTH values in patients with the hypercalcemic variant of hyperparathyroidism than in those with the normocalcemic variant were found both at enrollment and at the end of the observation period without *cinacalcet* (PTH at enrollment 191 ± 87.4 pg/ml for the hypercalcemic variant versus 99.9 ± 29.9 pg/ml for the normocalcemic variant, $p = 0.042$; PTH at the end of the observation period without *cinacalcet* 191.4 ± 80.5 pg/ml for the hypercalcemic variant versus 83.3 ± 13.6 pg/ml for the normocalcemic variant, $p = 0.011$).

Conversely, at the end of the observation period with *cinacalcet* no statistically significant difference between the mean values of PTH in the two variants of primary hyperparathyroidism was observed.

Finally, no statistically significant difference between the two variants of hyperparathyroidism for all other parameters taken into account, including the number and size of the stones, was found (Table 3).

Results of the t test for equality of means between females and males

T-test for equality of means between females and males led to the identification of a statistically significant difference only for the larger stone diameter that was greater in female subjects both at enrollment and at the end of the observation period with *cinacalcet* (larger diameter of stone at enrollment in female subjects: 0.94 ± 0.18 cm versus larger diameter of stone in males: 0.67 ± 0.15 cm; $p = 0.027$; larger diameter of stone at the end of the observation period with *cinacalcet* in female subjects: 0.71 ± 0.36 cm versus larger diameter of the stone after of the observation period with *cinacalcet* in males: 0.24 ± 0.24 cm; $p = 0.038$).

Adverse reactions of treatment

No problem related to adverse reactions or intolerance was reported in any of the two major therapeutic groups. **Tables posted in Supplementary Materials on www.aiua.it**

Discussion

This study, with the limits of a pilot trial conducted on a limited number of patients, shows, for the first time, the ability of *cinacalcet*, used in combination with a dietary regimen with a standardized intake of calcium, to reduce in a statistically significant way the total number of renal stones and the larger diameter of stones in patients with nephrolithiasis associated with primary hyperparathyroidism both in the normocalcemic and hypercalcemic variant. Our data also shows the ineffectiveness, within the same period of comparison, of the traditional therapeutic and dietary approach. The aforementioned variations in the number and size of renal stones with the use of *cinacalcet* resulted associated to changes in the endocrine and metabolic parameters, as widely expected, with a statistically significant reduction in serum calcium and parathyroid hormone and a statistically significant increase of serum phosphorus (PTH inhibits the tubular reabsorption of phosphorus and thus increases its urinary excretion) (21) and of urinary pH in the first morning urine (high levels of parathyroid hormone result in an initial transient renal acidosis which is offset by an increase in net acid excretion and the release of alkaline bases of bone resorptive origin) (22). As for the comparison between the two variants of hyperparathyroidism (normocalcemic and hypercalcemic), we observed, as expected, statistically significant higher values of serum calcium and statistically significant lower phosphorus values in patients with the hypercalcemic variant. Values of parathyroid hormone were significantly higher in patients with the hypercalcemic variant of hyperparathyroidism than in those affected by the normocalcemic variant although this difference disappeared at the end of the observation period *cinacalcet*. Absence of statistically significant difference between the mean values of parathyroid hormone in the two variants of hyperparathyroidism is a finding directly related to the use of *cinacalcet* at individually tailored dosages to achieve a normal range for PTH. Precisely, with the use of *cinacalcet* at an optimized dose for each patient in order to enable the achievement of values of parathyroid hormone in the normal range, as described above, and to maintain adequate values of calcemia, no statistically significant difference between the two forms of hyperparathyroidism in the number and size of stones was observed. Therefore, the above reported findings should be explained by *cinacalcet* administered in association with a diet standardized in calcium intake at a average daily dose of 48.86 ± 30.09 mg titrated in each patient to achieve values of parathormone within the normal range and serum calcium levels as well within the limits of the normal range. Obviously doses of *cinacalcet* were higher (and mostly refracted in two daily doses) in subjects suffering from the hypercalcemic variant of primary hyperparathyroidism (mean daily dose 63.75 ± 39.44 mg in

two doses in 75% of cases with the hypercalcemic variant versus 38.92 ± 20.02 in two doses in 50% of cases with the variant normocalcemic variant). As mentioned in the introduction, although a factor which contributes to the formation of stones in primary hyperparathyroidism is hypercalciuria, the urinary excretion of calcium per gram of creatinine do not necessarily differentiate patients who associate or not nephrolithiasis to primary hyperparathyroidism (7-9). Furthermore, although a high concentration of serum calcitriol linked to stimulation by PTH of renal hydroxylation of 25-hydroxyvitamin D, can contribute both to hypercalciuria and the formation of kidney stones, as shown in a study of 50 patients (23), this finding has to be confirmed because it was not observed in another study carried out in an even greater population (24). There are no differences in serum parathyroid hormone, calcium or calcitriol in patients with hyperparathyroidism with and without associated nephrolithiasis, though hypercalciuria is more often found in the group suffering from kidney stones (9, 25). This evidence is confirmed by the results of this study clearly showing that *cinacalcet* used in combination with a diet with standardized calcium intake (and not other treatment or dietary recommendations or the combination of both) has induced a reduction in the number and size of stones in association with a correction within normal limits of normality of parathyroid hormone without changes of other metabolic parameters taken into account (except for the increase of pH in the first morning urine). Significant changes in urinary calcium induced by *cinacalcet* were not expected in consideration of the mechanism of action of calcium mimetics that act as allosteric activators of the receptors for calcium by increasing the sensitivity of these to calcium ions (21). At renal tubular level the activation of the calcium-sensitive receptors leads to a reduction in the absorption of calcium and therefore to an increase in urinary calcium that appears counterbalanced however, in most patients, by the simultaneous decrease of the levels of PTH and serum calcium induced by the same treatment with calcium mimetics (21). The fractional excretion of calcium depends on the interaction between filtered load and tubular reabsorption and *cinacalcet* acts on both mechanisms, by reducing the first, through a reduction in serum calcium, and the second with its action in the distal tubular with a final net effect of substantially unchanged (1). This was confirmed, by example, in the study of *Crockett et al.* (26) where it was found that *cinacalcet* normalized serum calcium and safely lowered PTH without increasing the urinary excretion of calcium in the study subjects and so proving the potential benefit of this medical treatment for primary hyperparathyroidism. In the prospective study by *Peacock et al.* it was also reported minimal change in urinary calcium in patients treated with *cinacalcet* 30-60 mg daily, although there was a statistically significant reduction in fasting urinary calcium (14). Only patients carrying the polymorphism Arg990Gly of the calcium-sensitive receptor, that leads to a permanent increase in the sensitivity of these receptors, respond more strongly to *cinacalcet*, and could be exposed to an increased risk of nephrolithiasis during treatment with calcium mimetics (21).

CONCLUSIONS

It is not possible to draw other conclusions from our study, in particular for the limited number of subjects enrolled and the limited period of observation, other than in subjects suffering from nephrolithiasis in association with primary hyperparathyroidism (both normocalcemic and hypercalcemic, with exception of the carriers of the polymorphism Arg990Gly) the normalization of parathyroid hormone induced by *cinacalcet*, used in combination with a diet with normalized calcium intake, allows to control the "primary cause" of the renal stone complication and thus achieve, as long as you continue therapy, a concrete clinical advantage in terms of reduction in the number and size of stones, similarly to what can be definitely achieved, with greater certainty, by surgical parathyroidectomy that is definitely associated with a significant risk reduction of calcium stones, frequent remission or reduction of relapses (27, 28).

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