Alendronate in patients with calcium nephrolithiasis and loss of bone mass

Miguel Angel Arrabal-Polo*, Miguel Arrabal-Martín1, Salvador Arias-Santiago2, Armando Zuluaga-Gomez1

1 Urology Department, San Cecilio University Hospital, 18003 Granada, Spain
2 Medicine Department, Granada University, 18003 Granada, Spain

Received 8 December 2011; Accepted 3 April 2012

Abstract: Background. Our purpose is to show the effect of alendronate on patients with recurrent calcium lithiasis and loss of bone mass, and to observe their progress with analytical and densitometric markers. Methods. We present a unique cohort (before and after study) of 15 patients with recurrent calcium nephrolithiasis and loss of bone mass treated for three years with 70 mg sodium alendronate weekly. The sample is divided into two groups by sex (5 men and 10 women, aged 35–65 years). We assessed clinical progress of both bone and lithiasic disease and urine and plasma markers of both pathologies. Results. We obtained a significant decrease in calcuria levels after 3 years of treatment (15.1 vs. 10.1; p=0.01), fasting calcium/creatinine quotient (0.16 vs. 0.10; p=0.002), and β-crosslaps (0.596 vs. 0.501; p=0.01). Moreover, we observed a disease stabilization in 14 of the 15 patients (93.3%), and, in all patients, bone mineral density had improved. Neither side effects nor losses of patients were observed after 3 years of treatment. Conclusions. The use of weekly alendronate in patients with recurrent calcium lithiasis and loss of bone mass is safe and effective, curbs lithiasic disease progression, and improves bone mineral density.

Keywords: Alendronate • Calcium stones • Bone density loss

© Versita Sp. z o.o

1. Introduction

Calcium nephrolithiasis is the most common, diagnosed up to 75%–80% in patients with lithiasic disease. Its cause is multifactorial: it is related to urine PH alterations, anatomical alterations, metabolic alterations, and bone alterations [1,2]. Over the last five years, a relationship is increasingly being revealed among recurrent calcium nephrolithiasis, hypercalciuria, and loss of bone mass, either osteopenia or osteoporosis. This has also been shown through genetic studies in which sequence variations in the CLDN14 gene relate bone mineral density to nephrolithiasis [3]. Loss of bone mineral density (BMD) is a well-defined disease that appears when there is an alteration of the bone formation – destruction process with the formative balance becoming negative. BMD is measured by osteoblast activity in connection with osteoclasts, and must be equal to 1 in healthy adults; if there is an increase in osteoclast activity, it will be less than 1. Thanks to bone densitometry, we can classify patients as normal, osteopenic, or osteoporotic according to T-score values. Treatment for osteoporosis is in a constant state of renewal and update; it is important for treatment individualization depending on the case being treated. Through clinical trials and prospective studies, it has been proven that the use of bisphosphonates improves bone mineral density and avoids the onset of fractures [6,7].

Our purpose is to show the effect of alendronate on patients with recurrent calcium lithiasis and loss of
2. Material and methods

We conducted a prospective study with unique cohort (before and after study) in 15 patients (5 men and 10 women) with a 3-year follow-up period. We selected consecutive patients with calcium stones and bone mineral density loss in the period from June 2006 to September 2007 for inclusion in the work. There are more women in our study, because among the patients whom we studied in the established age range, the loss of bone mass is higher in women than that in men in an unselected group of patients. These patients presented recurrent calcium nephrolithiasis and loss of bone mass classified as osteopenia/osteoporosis according to bone densitometry. Osteopenia is defined by a punctuation T-score between -1 and -2.5 standard deviations (SD); osteoporosis by a punctuation T-score >-2.5 SD, and established osteoporosis, as > -2.5 SD plus fracture. Patients were treated with weekly sodium alendronate (70 mg/week). We consider recurrent calcium nephrolithiasis as two or more episodes of lithiasis in 2 years.

2.1. Inclusion and Exclusion Criteria

Men and women aged 35–65 years with recurrent calcium nephrolithiasis and loss of bone mass measured by bone densitometry (1 patient with osteoporosis, 11 patients with important osteopenia and 3 patients with mild osteopenia) were included in the study. Excluded were: patients treated with calcium, vitamin D, age younger than 35 years or older than 65 years, active hyperparathyroidism, distal renal tubular acidosis, congenital or acquired bone pathology, treatment with corticoids. Patients receiving treatment with diuretics (torasemide, furosemide, thiazides or others), receiving treatment with antihypertensives, and receiving treatment with pain killers on a regular basis were also excluded.

2.2. Methodology and Work Plan

At the beginning of this study, the patient is informed about the pathology and the start of treatment with weekly sodium alendronate (70 mg/week) for a minimum period of 3 years, with an explanation of possible side effects. The patient then gives consent to participate in the study. Arterial pressure, weight, height, and BMI are measured before starting medical treatment and at 2 years of treatment. Four lab tests are performed during treatment (basal, 1st year, 2nd year, and 3rd year), including, among others, serum parameters of interest (sodium, potassium, chlorine, calcium, phosphorus, alkaline phosphatase, PTH, osteocalcin, b-crosslaps, and 1.25 (OH) Vitamin D), and fasting and 24 hours urine parameters, among them (fasting calcium/creatinine quotient, calciuria, phosphaturia, oxaluria, citraturia, uricosuria, and magnesuria). Yearly imaging tests are done to assess clinical progress of the lithiasic disease (abdominal X-ray and ultrasound) and basal BMD, and also after 2 years of treatment with alendronate.

2.3. Study Variables

We assessed clinical progression of the lithiasic disease with imaging tests, progression of bone mineral density with a BMD test, progression of bone formation and resorption markers (osteocalcin, alkaline phosphatase, and B-crosslaps), calciuria, hypercalciuria, and fasting calcium/creatinine quotient after 3 years of treatment with bisphosphonates.

2.4. Statistical Study

A study of the results from the previously referred variables is conducted by applying non-parametric statistical tests (Wilcoxon) with SPSS 15.0 program for Windows.

2.5. Ethics

This study has been approved by our Hospital Ethics Committee after a presentation of the study objectives.

3. Results

At the beginning of treatment, 6 patients presented unilateral nephrolithiasis less than 2 cm; 6 had bilateral nephrolithiasis less than 2 cm; 1 patient had bilateral nephrolithiasis larger than 2 cm; and 2 patients had no residual lithiasis. All patients were asymptomatic; most lithiasis was located in lower calyx, but no instrumental treatment was required at that time. The median age of the patients was 52.5 ± 8.4 years. All study patients complied strictly with the treatment with weekly sodium alendronate during the 3-year follow-up period, without losses or side effects. (Table 1)
Lithiasis composition was: 1 case of calcium oxalate dihydrate lithiasis; 5, calcium oxalate monohydrate; 7, calcium oxalate monohydrate and dihydrate; and 2, calcium oxalate dihydrate with calcium phosphate.

### 3.1. Mineral and Bone Metabolism Study

Three lab tests (apart from the basal test) were performed to study mineral and plasma bone and urine metabolism during the 3-year follow-up. In plasma, we observed a statistically significant decrease in alkaline phosphatase values (60.8 vs. 50.7 at three years; p=0.01), in β-crosslaps values (0.596 vs. 0.101; p=0.001) (Figure 1), and a statistically significant increase in vitamin D levels (17.9 vs. 21.5 at three years; p=0.003). In urine, we detected statistically significant decrease in calciuria (15.1 vs. 10.1 at three years; p=0.01).
3.2. Clinical Progress of the Lithiasic Disease Study

All patients included in this study presented recurrent calcium lithiasic disease; only in one of the patients treated did we see a minimal growth of residual lithiasis (6.6%) but in all others, no modification of residual lithiasis occurred nor had de novo lithiasis formed. During the three years of treatment, no patient presented renal colic symptoms or pain in renal fossa (the patient did not use analgesics due to nephritic colic), being totally asymptomatic from the urological point of view (Table 1).

3.3. Bone Mineral Density Study

At the beginning of this study, 2 patients presented osteoporosis and 13 of them, osteopenia; the mean values for T-score from the bone densitometry were -1.4 in hip, -1.5 in femoral neck, and -2.1 in lumbar spine. At three years of treatment, compared with densitometry of the control, we observed a statistically significant improvement in the hip, femoral neck, and spine lumbar (-1.0; -1.2; -1.5; p<0.01) bone density (Table 2).

4. Discussion

Onset of loss of bone mass occurs along with progressive aging, thus, lithiasis has an increasing prevalence and incidence in parallel with increasing population longevity. However, male osteoporosis is currently underestimated [5]. The usual treatment for this disease can be done with different classes of drugs, among them, the bisphosphonates. The use of alendronate is widespread for the treatment of this pathology in chronic cases; the follow-up can be done by densitometry or bone markers [8–10]. Ravn et al showed that, by monitoring bone formation or resorption markers (osteocalcin, bone alkaline phosphatase, deoxypyridinoline, N-telopeptide, and C-telopeptide), it is possible to achieve good control of both disease progression and follow-up without performing bone densitometry [11]; Murphy et al also showed significant changes in bone markers after medical treatment with alendronate in patients with loss of bone mass [12]; we have reached the same conclusion in our study, but with a new bone resorption marker, the beta-crosslaps, observed a decrease in its levels along with an improvement in bone mineral density as measured by densitometry. It is important to closely monitor patients treated with bisphosphonates because undesirable effects have been described following extended treatment. Pazianas et al, nonetheless, in a wide review of jaw osteonecrosis, found only 26 cases of patients treated with bisphosphonates that presented such a side effect; this was a very low incidence in comparison with the large number of patients treated with these drugs worldwide [13]. Other side effects reported were atypical diaphyseal or subtrochanteric fractures after extended treatment but also with a very low incidence. In addition, cases of auricular fibrillation and gastrointestinal lesions have been described with a very low incidence; therefore, the benefit of treatment is much higher than the risk of side effects [14]. We have

---

Table 2. Evolution of the main parameters studied after 3 years of treatment with alendronate

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Basal ± SD</th>
<th>3 years alendronate ± SD</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.86±0.18</td>
<td>0.92±0.20</td>
<td>0.09</td>
</tr>
<tr>
<td>Sodium (mEq/l)</td>
<td>141.5±2.7</td>
<td>142.6±2.2</td>
<td>0.26</td>
</tr>
<tr>
<td>Potassium (mEq/l)</td>
<td>4.5±0.4</td>
<td>4.3±0.4</td>
<td>0.14</td>
</tr>
<tr>
<td>Chlorine (mEq/l)</td>
<td>100.86±2</td>
<td>100.86±3.6</td>
<td>1</td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>60.8±17.1</td>
<td>51.7±16.9</td>
<td>0.01</td>
</tr>
<tr>
<td>Calcium (mg/dl)</td>
<td>9.5±0.49</td>
<td>9.3±0.46</td>
<td>0.32</td>
</tr>
<tr>
<td>Phosphorus (mg/dl)</td>
<td>3.3±0.5</td>
<td>3.2±0.6</td>
<td>0.49</td>
</tr>
<tr>
<td>Magnesium (mmol/l)</td>
<td>0.9±0.2</td>
<td>0.9±0.3</td>
<td>0.90</td>
</tr>
<tr>
<td>iPTH (pg/ml)</td>
<td>56.9±18.3</td>
<td>56.9±22.7</td>
<td>0.86</td>
</tr>
<tr>
<td>Osteocalcin (ng/ml)</td>
<td>12.6±8.1</td>
<td>9.9±4.1</td>
<td>0.08</td>
</tr>
<tr>
<td>β-Crosslaps (ng/ml)</td>
<td>0.996±0.110</td>
<td>0.101±0.076</td>
<td>0.001</td>
</tr>
<tr>
<td>1,25 (OH) Vitamin D (µU/ml)</td>
<td>17.9±12.9</td>
<td>21.5±15.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Creatinine Clear (ml/min)</td>
<td>111.7±23.5</td>
<td>106.5±18.8</td>
<td>0.21</td>
</tr>
<tr>
<td>Diuresis (ml)</td>
<td>2243.3±546.3</td>
<td>2220±467.8</td>
<td>0.90</td>
</tr>
<tr>
<td>Calciumia (mg/dl)</td>
<td>15.1±8.1</td>
<td>10.1±5</td>
<td>0.01</td>
</tr>
<tr>
<td>Fosfaturia (mg/dl)</td>
<td>43.8±19.9</td>
<td>43.5±16.8</td>
<td>0.97</td>
</tr>
<tr>
<td>Uricosuria (mg/dl)</td>
<td>28.1±11.3</td>
<td>27±9.2</td>
<td>0.59</td>
</tr>
<tr>
<td>Oxaluria (mg/dl)</td>
<td>21.5±23.5</td>
<td>16.6±11</td>
<td>0.92</td>
</tr>
<tr>
<td>Magnesuria (mg/dl)</td>
<td>5.1±1.4</td>
<td>6±1.9</td>
<td>0.047</td>
</tr>
<tr>
<td>Citratura (mg/dl)</td>
<td>254.8±128.8</td>
<td>266.2±127.5</td>
<td>0.80</td>
</tr>
<tr>
<td>Fasting Ca/Creat</td>
<td>0.16±0.03</td>
<td>0.10±0.04</td>
<td>0.002</td>
</tr>
<tr>
<td>Hip BD (T-score)</td>
<td>-1.4±0.5</td>
<td>-1.0±0.5</td>
<td>0.001</td>
</tr>
<tr>
<td>Neck BD (T-score)</td>
<td>-1.5±0.4</td>
<td>-1.2±0.5</td>
<td>0.002</td>
</tr>
<tr>
<td>Spine BD (T-score)</td>
<td>-2.1±0.3</td>
<td>-1.5±0.3</td>
<td>0.001</td>
</tr>
</tbody>
</table>

SD: Standard desviation; Creatinine Clear: Creatinine clearance; BD: Bone densitometry; iPTH: intact parathohormone
M. A. Arrabal-Polo et al.

reported no side effects in the patients included in our study after 3 years of treatment with alendronate. It is true that prolonged use of alendronate may increase the risk of femur fracture, particularly in elderly patients [15]. However, in a study of 39,567 patients and 158,268 controls, it was observed that both small and large cumulative doses alendronate may increase the risk of femur fracture, so actually this effect may be a result of the osteoporosis already present and not of the drug [16]. It is true, however, that the absence of any side effects after 3 years of alendronate use in our study may be a result of small number of patients included.

Calcium nephrolithiasis and hypercalciuria are closely related to bone mineral loss in some patients. Genetic studies have revealed this relationship among CLDN14 gen modifications, osteoporosis, and nephrolithiasis [3]. For some years, thiazides have been used for treatment of calcium lithiasis with hypercalciuria, producing excellent results [17, 18]; but, it has also been observed that this therapy, although it decreases calciuria and with that the risk of nephrolithiasis formation, does not improve bone mineral density in comparison with usual supplements of calcium and vitamin D. Therefore, it is not indicated for monotherapy in patients with hypercalciuria, calcium lithiasis, and loss of bone mass [19]. The use of alendronate, nonetheless, has proven to decrease calciuria in combination with improvement in bone mineral density. Bushinsky et al showed in animal studies that bone calcium contributes in a significant way to increased calciuria and that the treatment with alendronate decreased the calcium supersaturation in urine significantly, thereby preventing the formation of calcium lithiasis [20]. Ruml et al demonstrated in patients with reduced mobility or immobility that alendronate inhibits bone resorption and avoids both hypercalciuria and the formation of oxalate or calcium phosphate crystals [21]. These results are similar to those in our study, in which a significant decrease in calciuria was observed along with a significant improvement of BMD and a significant stabilization of the lithiatic disease. Other studies also support our results regarding calciuria decrease and inhibition of bone resorption after treatment with alendronate [22, 23]. In 2007, our research group results in a first series of patients with heterogeneous bone pathology and calcium lithiasis in which we showed that the use of bisphosphonates alone or in combination with dyazides, in cases of high levels of calcium, brings the lithiatic disease to a significant halt and improved BMD as well [2].

The cost of treatment per patient with alendronate for 3 years is 399.88 euros, or 184.56 per year per patient. If we compare this cost with a session of extracorporeal shock wave lithotripsy or ureteroscopy, it is significantly lower [24]. Therefore, if we can prevent recurrent calcium nephrolithiasis with alendronate, we can obtain both important economic and health-saving effects.

Bisphosphonates in patients with recurrent calcium nephrolithiasis and loss of bone mass can be used alone or in combination with thiazides in case of hypercalciuria, but thiazides must not be used alone for treatment where there is loss of bone mass because they do not significantly increase BMD. Although the limitation of our study is the small number of patients included, we consider our results to be very important because the follow-up period is long, results are good and, in the literature, there are no similar references concerning clinical application of alendronate in patients with calcium lithiasis and osteopenia/osteoporosis.

5. Conclusion

The use of weekly sodium alendronate is a safe and effective treatment in patients with recurrent calcium nephrolithiasis and loss of bone mass, although further randomized clinical trials are necessary with a larger number of patients to corroborate our results with more data. In this initial study, with a single treatment group and a small number of patients, prolonged alendronate use was successful in treating calcium stones with BMD loss. This is a starting point for further studies that compare the effectiveness of this drug to others and a placebo to establish definitive conclusions.

Disclosure

Nothing to declare by all authors
No conflict of interest
No funding was received
References


