Alendronate and indapamide alone or in combination in the management of hypercalciuria associated with osteoporosis: a randomized controlled trial of two drugs and three treatments

Andrea Giusti1, Antonella Barone1, Giulio Pioli2, Giuseppe Girasole3, Vincenzo Siccardi3, Ernesto Palummeri1 and Gerolamo Bianchi3

1Department of Gerontology and Musculoskeletal Sciences, Galliera Hospital, Genoa, 2Geriatric Unit, ASMN, Reggio Nell’Emilia and 3Department of Reumatology, La Colletta Hospital, Arenzano, Italy

Abstract

Background. The role of bisphosphonates (BPs) in the management of patients with hypercalciuria (HC) associated with osteoporosis is still uncertain. The aim of the study was to evaluate the effect of alendronate and indapamide alone or in combination on bone mineral density (BMD) and 24-h urinary calcium excretion (24-CaU) in post-menopausal women with HC and low BMD.

Methods. A total of 77 post-menopausal women with HC (24-CaU > 4mg/kg/day) and low BMD [T-score < -2.0 at lumbar spine (LS), femoral neck (FN) or total hip (TH)] from two centres of Northern Italy were randomized to receive indapamide 2.5 mg daily alone (24 patients, IND group), alendronate 70 mg weekly alone (27 patients, ALN group) or the combination therapy (26 patients, ALN + IND group). Throughout the study, all subjects received daily calcium supplements, depending on their dietary intake, to maintain a daily input of 1000 mg. Patients were instructed to increase water intake up to 2000 mL daily. The percentage and absolute changes of BMD at LS, FN and TH, and the variation of 24-CaU from baseline at 1 year were the primary outcomes. Serum calcium, phosphate, parathyroid hormone and bone alkaline phosphatase were also measured.

Results. Overall 67 women completed the study and were included in the final analysis. Patients in the three groups were similar with regard to baseline characteristics. BMD did not significantly change from baseline after 1 year of treatment with indapamide (LS: +1 ± 3.1%; FN: −0.3 ± 3.5%; TH: −0.4 ± 3.1%), while it showed a significant increase from baseline in the other two groups (ALN; LS: +5.8 ± 4.2%, P < 0.001; FN: +3.9 ± 7.9%, P = 0.018; TH: +2 ± 3.6%, P = 0.006) (ALN + IND; LS: +8.2 ± 5.3%, P < 0.001; FN: +4.9 ± 6.7%, P = 0.007; TH: +2.9 ± 4.2%, P = 0.004). Patients in the combination group showed a significantly higher increase of BMD at LS compared to ALN (P = 0.04). After 1 year, 24-CaU values significantly decreased from baseline in all groups (IND, 239 ± 78 versus 364 ± 44, P < 0.001) (ALN, 279 ± 68 versus 379 ± 79, P < 0.001) (ALN + IND, 191 ± 68 versus 390 ± 55, P < 0.001). The mean percentage decrease of 24-CaU in ALN + IND group (−50%) was significantly greater compared to ALN (−24%, P < 0.001) and IND (−35%, P = 0.012).

Conclusions. These results show a benefit, in terms of BMD improvement and 24-CaU reduction, associated with BPs’ therapy in combination with indapamide in HC associated with osteoporosis. The combination therapy demonstrated a reduction of 24-CaU and an increase in LS BMD superior to that observed with alendronate alone. Our results support a new potential approach with BPs associated with thiazide diuretics or indapamide in the management of post-menopausal women with HC and associated bone loss. Studies on the larger sample size are needed to demonstrate the efficacy on the fracture outcome.

Keywords: alendronate; idiopathic hypercalciuria; indapamide; osteoporosis; treatment

Introduction

Idiopathic hypercalciuria (IHC) is defined as a 24-h urinary calcium excretion (24-CaU), in two consecutive collections, that exceeds 4 mg/kg/day, regardless of gender and in the absence of systemic diseases or pharmacological treatments that may cause normocalcemic hypercalciuria (e.g. sarcoidosis, vitamin D intoxication, hyperthyroidism) [1]. IHC occurs in ~5–10% of the general population and in 30–50% of patients with calcium kidney stones [1–3]. Although controversies still exist about the pathophysiological events responsible for hypercalciuria, a number of studies have suggested that bone cells involved in bone formation and resorption could play a central role in the chain of events leading to hypercalciuria, together with increased
intestinal calcium absorption and/or reduced renal tubular calcium reabsorption [4–7]. In fact, several investigators, in the last 10 years, have reported increased bone turnover and reduced bone mineral density (BMD) in subjects with IHC [6–11]. In addition, Melton et al. demonstrated, in a large population-based retrospective cohort study, a 4-fold increase in the risk of vertebral fractures among patients with calcium kidney stones [12]. On the other hand, Giannini and colleagues found that up to 19% of post-menopausal women with osteoporosis, referred for the first time to the Unit for Metabolic Bone Diseases, presented hypercalciuria [9].

Whether the decrease in BMD constitutes the primary event responsible for the hypercalciuria or its consequence, IHC is clearly associated with decreased bone mass, increased bone resorption, and may play a role in the pathogenesis of fragility fracture. Consequently, it has become important to test osteoporotic patients for IHC or conversely hypercalciuric subjects for low BMD, so as to implement strategies aimed at normalizing 24-CaU and improving BMD in subjects with this specific alteration [9].

Several studies demonstrated that thiazide diuretics and indapamide, with or without dietary intervention, may satisfactorily control hypercalciuria, prevent stone formation and, occasionally, produce a small increase in BMD, with a good profile of tolerability [1,6,13–19].

Bisphosphonates (BPs) are potent inhibitors of bone resorption and are well established as the leading drugs for the treatment of osteoporosis [20]. To date, a limited number of studies have investigated the role of BPs in the treatment of patients with hypercalciuria associated with osteoporosis, while there are no data available about the combination therapy of BPs with thiazide diuretics in the management of such condition [6,21–23].

The purpose of the present randomized controlled trial was to evaluate the effect of alendronate and indapamide alone or in combination on BMD and 24-CaU in post-menopausal women with hypercalciuria and low BMD.

Methods

Patients

The study population was recruited from two osteoporosis centres (Arenzano, Genova) within the same region (Liguria) of northern Italy between September 2003 and April 2006. Patients were eligible for inclusion in the study if they satisfied the following four criteria: were post-menopausal, community-dwelling, ambulatory women; were referred for the first time to a Center for Metabolic Bone Diseases; had a BMD T-score below −2 standard deviation (SD) in at least one of the three sites [lumbar spine (LS), femoral neck (FN) and total hip (TH)]; and had a 24-CaU measured in two consecutive collections, that exceeded 4 mg/kg/day, in the absence of systemic diseases or pharmacological treatments that might cause normocalcemic hypercalciuria [1].

Women already receiving anti-osteoporotic therapy (BPs, teriparatide, intact parathyroid hormone 1–84, calcium, vitamin D or its derivatives, strontium ranelate, fluoride salts, calcitomin, raloxifene), with secondary causes of osteoporosis, and with specific diseases (primary hyperparathyroidism, hyperthyroidism, renal tubular acidosis, medullary sponge kidney disease, multiple myeloma, sarcoidosis, hypercortisolism, liver or kidney failure, diabetes mellitus, severe gastrointestinal disorders, Paget’s disease of bone) or taking drugs (corticosteroids, anti-convulsants, levothyroxine, cyclosporine A, diuretics, aromatase inhibitors, thiazolidinediones) known to influence bone and calcium metabolism were excluded. All patients provided written informed consent before enrolment in the trial and the institutional review board at each centre approved the study.

Treatment protocol

Throughout the study, all subjects received daily calcium supplements, depending on their dietary intake, to maintain a daily input of 1000 mg. In addition, patients were instructed to increase water intake up to 2000 mL daily. No other dietary intervention was implemented. After the baseline blood, urine and BMD assessment, women were randomly assigned, using a computer-generated block randomization schedule, to receive alendronate 70 mg once-weekly alone (ALN), indapamide 2.5 mg once a day alone (IND) or alendronate 70 mg once a week plus indapamide 2.5 once a day (ALN + IND). Subjects were instructed to take alendronate in the morning under fasting conditions with a full glass of water (6–8 oz) and to remain in an upright position for 45 min before the first food or beverage of the day. Indapamide was taken once a day before breakfast. The investigators (AB, GG) involved in BMD measurement and analysis were unaware of treatment assignments throughout the study.

Data collection and measurements

All patients underwent a clinical history and physical examination. Age, weight, body mass index and age at menopause were recorded. Daily dietary calcium intake was assessed by a validated questionnaire [24]. Fasting blood and 24-h urine samples were obtained in all women once their daily calcium and water intakes were standardized (1000 mg day of calcium, 2 L of water). At baseline and at 12 months, serum intact PTH, total serum calcium, phosphate, 24-CaU, bone-specific alkaline phosphatase and serum albumin were evaluated. The 25-hydroxyvitamin D levels were assessed only at baseline. Calcium, phosphate, 24-CaU and albumin were measured using automated standard laboratory methods. Calcium levels were corrected for serum albumin concentration, using a validated formula [corrected calcium = measured serum calcium + 0.8 × (normal serum albumin – patient’s albumin)] [25].

Serum 25-hydroxyvitamin D3 (25-OHD) was measured by radioimmunoassay (RIA) using a commercial kit (detection limit 3.75 nmol/L; DiaSorin, Saluggia, Italy). Serum intact PTH 1–84 was assessed using an immunoradiometric method (DiaSorin) with a sensitivity of 0.7 pg/mL (normal range 12–72 pg/mL). The inter-assay coefficients of variation (CV) were between 8.2% and 11% for 25-OHD and between 3.4% and 4.9% for PTH (depending on the measured concentration). Bone-specific alkaline phosphatase was assessed using an enzyme-linked immunosorbent assay method (MetraBAP, Quidel Corporation, San Diego,
CA, USA) with a sensitivity of 0.7 U/L and an inter-assay CV of 5–8%.

In addition, serum potassium concentrations were measured at baseline, at 6 months and at the end of the study. Potassium was administered to indapamide subjects with hypokalaemia.

The BMD was measured at the anterior-posterior LS (L1-L4), FN and TH at baseline and at 12 months using dual-energy x-ray absorptiometry (Lunar Prodigy densitometer, GE Healthcare Technologies, Waukesha, WI, USA). The T-score was based on the normative database of the manufacturer. All the scans for each investigational site were done with the same machine. A quality-control programme was conducted throughout the study. The coefficients of variation of phantom scans were 0.39 and 0.42% for the Arenzano and Genova densitometers, respectively. Two investigators (AB, GG), who were blind to the treatment allocation, performed all BMD analyses separately.

Statistics

The percentage change of BMD at LS, FN and TH, and the variation of 24-CaU from baseline at 1 year were considered to be the primary outcomes.

The characteristics of the three groups were compared using the Mann–Whitney test for independent samples and repeated-measure analysis of variance for continuous data. Statistical inferences were made on the basis of a two-sided significance level of $P < 0.05$. All analyses were performed in SPSS, version 12.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Characteristics of study patients

A total of 77 woman matching inclusion criteria were enrolled and randomized for the study, 67 patients (87%) completed the 12-month therapy and were included in the analysis. Ten subjects withdrew for different reasons: 9 dropped out because of adverse events and 1 for protocol violations (Figure 1). There was no statistically significant difference in baseline characteristics between patients lost to follow-up and subjects included in the final analysis (data not shown). The three groups were similar with regard to the baseline characteristics (Table 1). The mean age $\pm$ SD was 62.7 $\pm$ 6.1 years, with a quite wide range (52–79 years). The mean baseline BMD $T$-score $\pm$ SD at LS, FN and TH was $-2.9 \pm 1.3$, $-2.1 \pm 0.9$ and $-1.8 \pm 0.6$, respectively. Twelve women (four ALN group, three IND group, five ALN + IND group) had a history of symptomatic nephrolithiasis, but none experienced any episode during the study period.

BMD changes under treatment (Table 2 and Figure 2)

The BMD did not significantly change from baseline after 1 year of treatment with indapamide, but showed a significant increase from baseline in the other two groups (Table 2). As shown in Figure 2, subjects treated with the combination therapy or with alendronate alone demonstrated, at the end of follow-up, a significantly higher mean percent increase of BMD at LS (A), FN (B) and TH (C) than those receiving indapamide alone. In addition, patients allocated to ALN + IND showed a significantly greater improvement of BMD at LS compared to those randomized to ALN alone ($P = 0.04$), while a not significant but similar trend between the two groups (ALN + IND versus ALN) was found at FN and TH (Figure 2A, B and C).

Laboratory test results (Table 2 and Figure 3)

After 1 year, all three groups showed a statistically significant absolute reduction of 24-CaU from baseline (Table 2). As shown in Figure 3, the decrease in the combination therapy group was significantly greater with respect to ALN alone and indapamide alone ($P < 0.001$).
Table 1. Baseline characteristics of the patients who completed 12 months of therapy and were included in the analysis according to the treatment group

<table>
<thead>
<tr>
<th>Baseline characteristic</th>
<th>ALN (n = 25)</th>
<th>IND (n = 20)</th>
<th>ALN + IND (n = 22)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.2 ± 5.6</td>
<td>62.9 ± 6.1</td>
<td>62.0 ± 6.8</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>59.8 ± 7.4</td>
<td>56.0 ± 7.8</td>
<td>60.1 ± 7.4</td>
<td>NS</td>
</tr>
<tr>
<td>BMI (Kg/m²)</td>
<td>24.5 ± 3.1</td>
<td>23.4 ± 4.0</td>
<td>24.8 ± 2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Age at menopause (years)</td>
<td>50.4 ± 4.3</td>
<td>47.6 ± 3.7</td>
<td>47.8 ± 9.8</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium intake (mg/day)</td>
<td>874 ± 192</td>
<td>888 ± 207</td>
<td>863 ± 171</td>
<td>NS</td>
</tr>
<tr>
<td>Lumbar spine BMD (g/cm²)</td>
<td>0.759 ± 0.088</td>
<td>0.843 ± 0.113</td>
<td>0.793 ± 0.112</td>
<td>NS</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²)</td>
<td>0.677 ± 0.131</td>
<td>0.697 ± 0.088</td>
<td>0.675 ± 0.117</td>
<td>NS</td>
</tr>
<tr>
<td>Total hip BMD (g/cm²)</td>
<td>0.755 ± 0.111</td>
<td>0.765 ± 0.070</td>
<td>0.749 ± 0.089</td>
<td>NS</td>
</tr>
<tr>
<td>Serum calciuma (mg/dL)</td>
<td>9.3 ± 0.4</td>
<td>9.5 ± 0.3</td>
<td>9.2 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL)</td>
<td>3.5 ± 0.4</td>
<td>3.4 ± 0.5</td>
<td>3.4 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>24-h urinary calcium (mg/24 h)</td>
<td>379 ± 79</td>
<td>364 ± 44</td>
<td>390 ± 55</td>
<td>NS</td>
</tr>
<tr>
<td>Parathyroid hormoneb (pg/mL)</td>
<td>60.0 ± 18.9</td>
<td>54.2 ± 20.5</td>
<td>62.1 ± 20.1</td>
<td>NS</td>
</tr>
<tr>
<td>Bone alkaline phosphataseb (U/L)</td>
<td>24.8 ± 5.6</td>
<td>29.0 ± 9.4</td>
<td>23.2 ± 12.6</td>
<td>NS</td>
</tr>
<tr>
<td>25-hydroxyvitamin D³ (nmol/L)</td>
<td>22.9 ± 13.5</td>
<td>22.9 ± 8.7</td>
<td>26.5 ± 12.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

aSerum calcium is measured calcium level corrected for serum albumin concentration.
bDetermined in serum.

Normal values for laboratory measures: parathyroid hormone, 12–72 pg/mL; calcium, 8.5–10.5 mg/dL; phosphate, 2.5–4.5 mg/dL; bone alkaline phosphatase, 14.2–42.7 U/L; 24-h urinary calcium, < 4 mg/kg/24 h.

ALN, alendronate alone; IND, indapamide alone; ALN + IND, alendronate plus indapamide; BMI, body mass index; BMD, bone mineral density; h, hours.

Fig. 2. Percentage changes (mean ± standard deviation) in bone mineral density (BMD) at lumbar spine (A), femoral neck (B) and total hip (C), from baseline at 12 months in patients treated with alendronate alone (ALN), indapamide alone (IND) or alendronate plus indapamide (ALN + IND).

Serum calcium (mg/dL ± SD) demonstrated a significant increase from baseline at 12 months only in subjects in the IND group (Table 2). However, repeated measures of ANOVA found no significant difference in calcium variation between the three groups (P = 0.159).

Interestingly, after 1 year, intact PTH (pg/mL ± SD) showed a significant reduction from baseline in the combination group, while opposite but not significant changes were found from baseline in the other two groups (Table 2). As shown in Table 2, phosphate did not change from baseline in the three groups after 12 months. Finally, as expected, bone-specific alkaline phosphatase demonstrated a significant reduction at 1 year in women who received alendronate alone or in combination, but did not show a significant change in the indapamide group (Table 2).
We found a significant increase of BMD from baseline after 12 months in subjects receiving alendronate alone or in combination with indapamide, while IND alone failed to improve BMD. It must be noted that studies about the effect of thiazide diuretics and indapamide on BMD in subjects with IHC yielded to conflicting results [13–19]. In contrast with findings by Pak et al. that documented a beneficial effect of thiazides or indapamide on BMD in subjects with IHC, our work, consistent with the trial by Legroux-Gerot and colleagues, does not support the positive effect of thiazide or indapamide on BMD [13–14]. These results are similar to two other investigations designed to assess the effect of BPs’ therapy on BMD in subjects with IHC [22–23]. Heilberg and colleagues demonstrated that etidronate, given to young, calcium stone-forming males presenting with hypercalciuria and osteopenia, led to a significant amelioration of BMD, evident only in the LS after 1 year of treatment [22]. Similarly, Weisinger et al. found a benefit of alendronate therapy on LS BMD in hypercalciuric not osteoporotic subjects [23].

One of the most relevant findings of the present study is the fact that women receiving ALN + IND showed a significantly greater increase of LS BMD compared to women treated with alendronate alone. A similar trend was found for FN and TH, even if not significant, probably due to the limited number of subjects enrolled.

### Table 2. Mean ± Standard deviation values of the variables measured at baseline and after 12 months of treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>ALN</th>
<th>P-value</th>
<th>IND</th>
<th>P-value</th>
<th>ALN + IND</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumbar spine BMD (g/cm²) baseline</td>
<td>0.759 ± 0.88</td>
<td>&lt;0.001</td>
<td>0.843 ± 0.113</td>
<td>NS</td>
<td>0.793 ± 0.112</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Lumbar spine BMD (g/cm²) 12 months</td>
<td>0.801 ± 0.82</td>
<td>0.018</td>
<td>0.851 ± 0.113</td>
<td>NS</td>
<td>0.856 ± 0.103</td>
<td>0.007</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²) baseline</td>
<td>0.677 ± 0.131</td>
<td>0.018</td>
<td>0.697 ± 0.088</td>
<td>NS</td>
<td>0.675 ± 0.117</td>
<td>0.007</td>
</tr>
<tr>
<td>Femoral neck BMD (g/cm²) 12 months</td>
<td>0.699 ± 0.117</td>
<td></td>
<td>0.694 ± 0.087</td>
<td>NS</td>
<td>0.704 ± 0.106</td>
<td></td>
</tr>
<tr>
<td>Total hip BMD (g/cm²) baseline</td>
<td>0.755 ± 0.111</td>
<td>0.006</td>
<td>0.765 ± 0.070</td>
<td>NS</td>
<td>0.749 ± 0.089</td>
<td>0.004</td>
</tr>
<tr>
<td>Total hip BMD (g/cm²) 12 months</td>
<td>0.770 ± 0.114</td>
<td></td>
<td>0.761 ± 0.068</td>
<td>NS</td>
<td>0.770 ± 0.096</td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mg/dL) baseline</td>
<td>9.3 ± 0.4</td>
<td>NS</td>
<td>9.5 ± 0.3</td>
<td>.021</td>
<td>9.1 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum calcium (mg/dL) 12 months</td>
<td>9.3 ± 0.4</td>
<td>NS</td>
<td>9.7 ± 0.5</td>
<td>NS</td>
<td>9.3 ± 0.3</td>
<td>NS</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL) baseline</td>
<td>3.5 ± 0.4</td>
<td>NS</td>
<td>3.4 ± 0.5</td>
<td>NS</td>
<td>3.4 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Serum phosphate (mg/dL) 12 months</td>
<td>3.4 ± 0.4</td>
<td></td>
<td>3.2 ± 0.5</td>
<td>NS</td>
<td>3.3 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>24-CaU (mg/24 h) baseline</td>
<td>379 ± 79</td>
<td>&lt;0.001</td>
<td>364 ± 44</td>
<td>&lt;.001</td>
<td>390 ± 55</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>24-CaU (mg/24 h) 12 months</td>
<td>279 ± 68</td>
<td></td>
<td>239 ± 78</td>
<td></td>
<td>191 ± 68</td>
<td></td>
</tr>
<tr>
<td>Serum PTH (pg/mL) baseline</td>
<td>60.0 ± 18.9</td>
<td>NS</td>
<td>54.2 ± 20.5</td>
<td>NS</td>
<td>62.1 ± 20.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Serum PTH (pg/mL) 12 months</td>
<td>63.7 ± 25.6</td>
<td></td>
<td>47.5 ± 12.8</td>
<td></td>
<td>45.9 ± 14.7</td>
<td></td>
</tr>
<tr>
<td>Serum BAP (U/L) baseline</td>
<td>24.8 ± 5.6</td>
<td>0.005</td>
<td>29.0 ± 9.4</td>
<td>NS</td>
<td>23.2 ± 12.6</td>
<td>0.042</td>
</tr>
<tr>
<td>Serum BAP (U/L) 12 months</td>
<td>19.2 ± 6.4</td>
<td></td>
<td>29.4 ± 8.0</td>
<td></td>
<td>18.8 ± 9.3</td>
<td></td>
</tr>
</tbody>
</table>

*Serum calcium is measured calcium level corrected for the serum albumin concentration.

ALN, alendronate alone; IND, indapamide alone; ALN + IND, alendronate plus indapamide; BMD, bone mineral density; 24-CaU, 24-h urinary calcium excretion; PTH, parathyroid hormone; BAP, bone alkaline phosphatase.

### Discussion

The current randomized controlled trial has been designed to evaluate whether the combination of alendronate plus indapamide would produce greater benefits on BMD and 24-CaU compared to alendronate or indapamide alone, in post-menopausal women with hypercalciuria associated with osteoporosis.

As expected indapamide demonstrated to be a potent inhibitor of urinary calcium excretion, even though alendronate alone induced a significant, albeit lower, reduction in 24-CaU. Women in combination therapy experienced the highest reduction of urinary calcium excretion, resulting in an additional effect of the two drugs. The beneficial effect of the BP on 24-CaU, in the absence of other dietetic or therapeutic intervention, indirectly support the role of bone cells and bone resorption in the pathogenesis of the excessive calcium excretion in IHC, as it was suggested years ago by Pacifici and others [4–6,21].
This is the first randomized controlled study designed to assess the effect of a combination therapy of ALN + IND on post-menopausal women with hypercalciuria associated with osteoporosis. In fact, only a minority of previous studies on this topic were randomized and none used a BPs [13–19,21–23]. Moreover, all published trials compared the effect of a single therapy in observational or randomized versus placebo study, while this work was undertaken to describe the effect on 24-CaU and BMD of a BPs combined with hypocalciuric diuretic.

This work has several limitations. The first is the small sample size, even if comparable to other studies on IHC. Probably due to this issue, it was not possible to demonstrate a significantly greater effect of the combination therapy on FN and TH BMD. On the basis of these data, it is therefore possible to support a significant benefit on BMD only at LS. Another limitation arises from the fact that the subjects were not classified according to the pathogenesis of hypercalciuria—fasting or absorptive. A different effect of the combination therapy could have been demonstrated on the two subtypes, the role of bone in their pathogenesis probably being different. Controversies have arisen as to whether bone involvement is relative to all hypercalciuric patients or only to those with fasting hypercalciuria, but it must be pointed out that in recent years bone involvement was demonstrated even in absorptive hypercalciuria [6–8,10,11,27,28]. Therefore, further randomized controlled trials are needed to evaluate whether the combination therapy could have been demonstrated on both the subtypes of IHC. Finally, a more detailed assessment of bone turnover, including bone resorption markers, would help to better understand the bone involvement in the two subtypes of hypercalciuria, as well as the contributing mechanism of the two drugs on the whole effect.

In conclusion, our results support a new potential and more beneficial approach with BPs associated with indapamide in the management of post-menopausal women with hypercalciuria associated with osteoporosis.

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Conflict of interest statement. None declared.

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