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Prevention of Osteoporosis

Four-Year Follow-Up of a Cohort of Postmenopausal Women Treated with an Ossein-Hydroxyapatite Compound

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Abstract

Background: The long-term effects of ossein-hydroxyapatite compound (OHC), a drug used for osteoporosis prevention, have not been previously reported. The aim of this study was to assess the long-term efficacy of OHC in postmenopausal women with bone mineral density (BMD) in the osteopenia range.

Methods: We performed a retrospective 4-year follow-up study in a primary-care setting to assess changes in BMD in a cohort of 112 postmenopausal women included in an osteoporosis programme that included health and dietary advice and who were treated with OHC 1660mg every 12 hours. BMD was measured annually in the distal part of the forearm, with T- and Z-score values being calculated for trabecular and total bone.

Results: A progressive and statistically significant increase in BMD was observed in trabecular and total T- and Z-score mean values. At baseline, mean ± SD trabecular T- and Z-scores were −1.27 ± 0.7 and −1.03 ± 0.7, respectively, and −0.86 ± 0.7 and −0.62 ± 0.7, respectively, at the end of the 4-year follow-up period (both $p < 0.0001$). Mild constipation was observed in 3.2% of patients during the follow-up period.

Conclusion: Ossein-hydroxyapatite compound could be an effective and safe agent for the prevention of bone loss in postmenopausal osteopenic women, with significant increases in BMD being observed in this group of patients.

Introduction

The prevalence of osteoporosis in the Spanish female population, as in other European countries,[1] is about 13%,[2] but this percentage increases to 35% in women aged ≥50 years.[3] Despite this high prevalence, the proportion of women receiving preventive treatment remains very low as osteoporosis is underdiagnosed and undertreated worldwide.[4-8]

There are several drugs that prevent bone mass loss and reduce the risk of fractures secondary to bone fragility,[9] but it is important to choose the most appropriate treatment for each patient in order to obtain an acceptable risk/benefit ratio. Two studies carried out in young postmenopausal women treated with either vitamin D and calcium[10] or alendronic acid[11] showed significant bone mass loss in the placebo groups compared with actively

treated groups, suggesting the value of preventive treatment in young postmenopausal women.

Osseïn-hydroxyapatite compound (OHC) has shown efficacy, either as monotherapy[12] or when combined with hormone replacement therapy (HRT),[13] in maintaining bone mineral density (BMD) and preventing postmenopausal osteoporosis. OHC has also been shown to be effective in the prevention of corticosteroid-induced osteoporosis.[14,15] In these situations (postmenopausal osteoporosis and corticosteroid-induced osteoporosis), significant bone mass maintenance was observed in women treated with OHC, compared with bone mass loss observed in patients treated with calcium carbonate or in the control group. Moreover, an increase in BMD was obtained when OHC was used in combination with other drugs (e.g. HRT and vitamin D).

An 830mg tablet of OHC is made up of: calcium 178mg, phosphorus 82mg and bone metabolism proteins (osteocalcin 5.8μg; type I collagen 216mg; insulin-like growth factor I [IGF-I] 168ng; IGF-II 84ng; transforming growth factor β [TGF-β] 21ng). The organic components of OHC have been shown to have significant effects on bone regeneration in experimental studies, suggesting an osteogenic action.[16,17] Other studies suggest that OHC is able to stimulate bone metabolism,[18] particularly when osteoblastic activity is reduced. This effect might be related to osteoblast stimulation and proliferation, in which growth factors such as TGF-β[19] and IGF-I[20] have been implicated.

Because of a lack of data about the long-term efficacy of OHC in preventing bone loss in postmenopausal women, the present retrospective study was carried out to investigate the progression of BMD over 4 years in a group of patients with a mean baseline BMD value within the osteopenic range who were treated with OHC. The subjects were participating in a menopause programme (see next section) conducted by a primary-care centre in Madrid.

Material and Methods

The women included in the study are from the Tetuan and Chamartin Madrid districts. All are voluntary participants in a menopause programme conducted by Centro Madrid Salud Tetuan (CMST). The programme, which is promoted by the Madrid City Council, started in 1994 and is ongoing.

The programme includes interventions intended to assist menopausal women by preventing and/or treating clinical issues of high prevalence during this period (e.g. osteoporosis, cardiovascular risk, climacteric symptomatology) and screening for breast cancer and gynaecological cancers. Each woman also reports the amount of dairy products consumed, which allows an estimation of dietary calcium ingestion, and steps are taken to increase physical exercise.

The programme includes women aged 45–55 years, younger women with spontaneous or surgical menopause, and older women whose last menstruation took place within the previous 5 years. Any woman with the above characteristics who resides in the town where the programme is being conducted may participate.

At inclusion, each participant provides a complete history and undergoes a full physical and gynaecological examination, together with additional examinations, such as laboratory investigations (general and hormonal parameters), mammography, pelvic ultrasonography, bone densitometry and cytology, when needed. All participants also receive three educational lectures on menopause, which includes a revision of healthy dietary habits specific to the menopause and a strong recommendation to participate in regular exercise. Subsequent examinations are performed annually, except when a participant needs specific attention on a more frequent basis.

A cohort of 112 women who had received two tablets of OHC (Osteopor®, 830mg per tablet, Pierre Fabre Médicament Production, France)[1] twice daily orally and had a self-reported therapeutic compliance of >80% was selected from all participants in

1 The use of trade names is for product identification purposes only and does not imply endorsement.

the programme. Compliance was self-reported by participants, who were asked to describe how often they were taking the medication at recommended dose in terms of the following possible responses: 'always', 'almost always', 'half the time', 'sometimes', 'never'. Only participants answering 'always' and 'almost always' were included in the analysis.

OHC was prescribed for one of the following reasons: the patient had a BMD below normal according to WHO criteria (T-score ≤−1 SD) or had a normal BMD but dietary calcium ingestion was inadequate and good compliance with an improved diet could not be expected. Treatment with an antireabsorptive drug was recommended when the woman had a T-score <−2 SD, but if the patient stated that she did not want antireabsorptive therapy, OHC was proposed instead.

All participants were followed up for 4 years. Baseline densitometry data from the ultradistal radius with T- and Z-score determinations in trabecular and total bone were available for all participants. BMD measurements were carried out in the distal radius according to the peripheral quantitative computed tomography (pQCT) technique, using a STRATEC® densitometer XCT-960. The coefficient of variation (CV) of this densitometer is 2%. BMD was expressed as T-score and Z-score values, which were automatically obtained from the densitometer according to data provided by the manufacturer. Adverse effects during the follow-up period were also documented.

Statistical Analysis

Descriptive statistics were applied to collected variables. Qualitative variables were described using percentages; quantitative variables were described using mean, SD and 25th and 75th percentiles. BMD progression in the cohort during the 4 years was evaluated by Friedman's test for paired data. The significance level was set at $p < 0.05$ in all tests. The statistical analysis was performed with SAS package version 8.2.

Results

At baseline, the mean age of this cohort was 51.5 ± 2.3 years. A baseline description of the patients' characteristics is shown in table I.

Table II shows baseline T- and Z-score values from trabecular and total bone for the cohort. The mean ± SD value of trabecular T scores for this group was −1.27 ± 0.7, which suggests that most participants were osteopenic.

The BMD values for trabecular and total bone documented during the 4 years of the study are shown in table III. The cohort displayed a significant increase in trabecular and total bone mass for both T- and Z-scores ($p < 0.0001$). For trabecular bone, a mean ± SD increase of 0.41 ± 0.2 on baseline values was observed for both T- and Z-score values. For total bone, the mean increases were 0.46 ± 0.3 and 0.39 ± 0.15 for T- and Z-scores, respectively.

The increase in BMD tended to be more pronounced after the first year of treatment. No women in the study received, either before or during the study, any compound other than OHC with a known influence on bone metabolism.

The tolerability of OHC was excellent. The most frequent adverse reaction was occasional mild constipation, which was experienced in 3.2% of women. One woman (0.8%) experienced heartburn, which was completely relieved by temporary ad-

Table I. Baseline characteristics of the study cohort (n = 112)

Variable	n	%
Family history of osteoporosis	58	51.8
Personal history		
diabetes mellitus	3	2.7
bone pain	100	89.3
Lifestyle characteristics		
smoker	29	25.9
takes exercise	45	40.2
alcohol intake (<15–30 g/day)	2	1.8
dairy product intake[a]		
milk	104	92.9
yoghurt	36	32.1
cheese	10	8.9
other dairy products	2	1.8

a Consuming the product at least once daily.

Table II. Baseline T- and Z-scores (trabecular and total bone) for the cohort (n = 112)

Variable	Score
Trabecular bone	
T-score (mean ± SD)	−1.27 ± 0.7
$Q_1 - Q_3$[a]	−1.7 to −0.8
Z-score (mean ± SD)	−1.03 ± 0.7
$Q_1 - Q_3$[a]	−1.5 to −0.7
Total bone	
T-score (mean ± SD)	−0.67 ± 0.9
$Q_1 - Q_3$[a]	−1.3 to 0.0
Z-score (mean ± SD)	−0.17 ± 1.0
$Q_1 - Q_3$[a]	−0.8 to 0.5

a 25th and 75th percentiles.

ministration of antacids and did not require interruption of OHC medication.

Discussion

Given the high prevalence of osteoporosis[21,22] in developed countries, particularly in postmenopausal women, and the progressive demographic aging of the population in the so-called 'first world', it is essential to implement preventive measures for osteoporosis as recommended by WHO[23] together with therapeutic measures once osteoporosis is established.

To our knowledge, this study is the first to evaluate the efficacy and tolerability of OHC over a 4-year period in a group of women with mild osteopenia. The present study found interesting results with regard to the progression of BMD in a group of postmenopausal women treated with OHC in everyday clinical practice. Long-term follow-up in this study seemed to suggest that bone mass increase does not take place uniformly throughout the 4-year period, with a more pronounced increase being observed after the first year of therapy.

The absence of standardised comparisons of fracture risk when different equipment and bone site locations are used can be seen as a limitation of this study, in which measurements were taken from the forearm only. Nevertheless, application of the pQCT technique at this location allowed the detection of a significant mean increase in BMD in the study group ($p < 0.0001$). These results might support the use of OHC as a means of preventing bone mass loss, as has been previously suggested.[12,24]

Furthermore, the results of the present study, in which BMD in OHC-treated women increased over a 4-year period, are consistent with those of three previous randomised studies,[12,13,24] in which BMD was seen to be maintained in the OHC group (indicating no bone loss with OHC) while decreasing in comparator groups. One of these studies[12] was a 2-year follow-up, open-label, prospective, parallel-design clinical trial conducted in postmenopausal women with normal baseline BMD. In this study, mean lumbar BMD (measured by dual-energy x-ray absorptiometry) in the OHC group remained stable throughout the study, whereas a significant decrease was observed in the group treated with calcium carbonate (−3.7%, $p < 0.05$) and in the treatment-free control group (−5.6%, $p < 0.01$). It is also interesting to note that in this study the administered daily dose of calcium was lower in the OHC group than in the calcium carbonate group (712mg vs 1000mg, respectively), a finding that reinforces the idea that the efficacy of OHC could be determined not only by its mi organic fraction of

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Table III. Change in bone mineral density in trabecular and total bone over the 4-year study period in the cohort (n = 112)

Year	Trabecular bone		Total bone	
	T-score (mean ± SD)	Z-score (mean ± SD)	T-score[a] (mean ± SD)	Z-score (mean ± SD)
Baseline	−1.27 ± 0.7	−1.03 ± 0.7	−0.67 ± 0.9	−0.17 ± 1.0
1	−1.20 ± 0.7	−0.96 ± 0.7	−0.55 ± 0.9	−0.06 ± 1.0
2	−1.08 ± 0.7	−0.84 ± 0.7	−0.45 ± 0.9	0.02 ± 0.9
3	−0.97 ± 0.7	−0.69 ± 0.8	−0.33 ± 0.9	0.15 ± 0.9
4	−0.86 ± 0.7[b]	−0.62 ± 0.7[b]	−0.21 ± 0.9[b]	0.22 ± 0.9[b]

a Sample size was 111 for this measure.

b $p < 0.0001$, Friedman's test.

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cohort (n = 112)

Z-score (mean ± SD)
−0.17 ± 1.0
−0.08 ± 1.0
0.02 ± 0.9
0.15 ± 0.9
0.22 ± 0.9[b]

not only by its mineral content[25] but also by the organic fraction of the compound.

A second study[24] compared the efficacy of OHC and calcium carbonate (with equivalent calcium doses) in postmenopausal women who presented with osteoporosis and one or more vertebral fractures. Maintenance of peripheral trabecular BMD in the group treated with OHC was observed, compared with a significant loss of trabecular BMD in the calcium carbonate group.

In the third study,[13] which evaluated OHC as part of a combined treatment with HRT over 1 year, significant bone mass loss was observed in the control group treated with calcium carbonate only, whereas BMD values remained stable through the study in the group treated exclusively with OHC. Another group, treated with a combination of HRT and OHC, showed a significant increase in BMD value (4.7%), which was higher than that obtained with HRT alone (2.2%).

As these studies included patients with different baseline characteristics or used different BMD measurement methods, their results cannot be directly compared with those of the present study. However, a similar trend is observed, which might contribute support to the idea that OHC could be efficacious in different clinical situations.

Another limitation of this study is that its retrospective design means that direct comparison of its results with those of prospective studies is not possible. Furthermore, it was not possible to create a control group with the same characteristics as OHC users in this study because the treatment protocol was proposed for osteopenic women in our centre. Moreover, while the results observed in this study should be confirmed in a long-term randomised controlled study, it is important to note that the data obtained in this study were for patients in whom reported treatment compliance was >80% and who had completed 4 years of follow-up.

Interestingly, we also analysed progression of BMD in a group of 125 women included in the same menopause programme but who did not receive treatment for osteoporosis because they had normal BMD (data not included in the present report). Despite following the same type of control and dietary advice, the untreated group showed a constant and significant decrease in mean trabecular bone T-score decrease, from 0.30 ± 0.8 SD to −0.08 ± 0.8 SD ($p < 0.0001$) over the same 4-year follow-up period. Even though the two cohorts are not comparable because their baseline BMD values were different, this observation could provide some insight into the expected evolution of bone mass in postmenopausal women and the need for close observation of BMD to prevent development of osteoporosis.

Conclusion

In this retrospective, non-comparative study, the observed increase in bone mass during the 4-year follow-up period in the group treated with OHC, together with good drug tolerability, suggests that prolonged treatment with OHC at the indicated dosage might be of value in preventing bone mass loss in postmenopausal women with a limited intake of dietary calcium and T-score values in the range of mild osteopenia.

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Abstract