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Efficacy of ossein-hydroxyapatite complex compared with calcium carbonate to prevent bone loss: a meta-analysis

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Abstract

Objective: There is increasing evidence to suggest that ossein-hydroxyapatite complex (OHC) is more effective than calcium supplements in maintaining bone mass. The aim of this meta-analysis was to determine whether OHC has a different clinical effect on bone mineral density (BMD) compared with calcium carbonate (CC).

Methods: A meta-analysis of randomized controlled clinical trials was carried out to evaluate the efficacy of OHC versus CC on trabecular BMD. We identified publications on clinical trials by a search of electronic databases, including MEDLINE (1966-November 2008), EMBASE (1974-November 2008), and the Cochrane Controlled Clinical Trials Register.The primary endpoint was percent change in BMD from baseline. Data were pooled in a random-effects model, and the weighted mean difference was calculated. A sensitivity analysis that excluded trials without full data was performed.

Results: Of the 18 controlled trials initially identified, 6 were included in the meta-analysis. There was no significant heterogeneity among the included trials. The percent change in BMD significantly favored the OHC group (1.02% [95% CI, 0.63-1.41], $P < 0.00001$). These results were confirmed in the sensitivity analysis.

Conclusions: OHC is significantly more effective in preventing bone loss than CC.

Key Words: Bone mineral density – Calcium carbonate – Meta-analysis – Ossein-hydroxyapatite complex – Osteoporosis prevention.

Several studies have demonstrated an association between bone mineral density (BMD) levels and fracture risk,[1-3] although there is currently no agreement on the extent to which increases in BMD contribute to reducing fracture risk.[4,5] Calcium salts can increase BMD, although to a lesser extent than some antiresorptive drugs, and it is not clear whether they help to prevent fractures.[6-8] In addition to increased BMD, other factors may play a role in determining bone quality and fracture risk. These include the conservation of trabecular and connective tissue, bone microarchitecture, the degree of biochemical replacement, and the thickness of the cortical tissue.[9] It is generally agreed that calcium should be administered to patients with osteopenia or osteoporosis.[10] In patients with osteoporosis, calcium is often given in addition to other treatments.

Ossein-hydroxyapatite complex (OHC) is also used to prevent and treat osteoporosis and to regulate the calcium-phosphorus balance in situations such as pregnancy and breast-feeding or as an adjuvant therapy to accelerate consolidation of bone fractures. It has been particularly widely researched and used in the prevention and treatment of osteoporosis.

The components of OHC have shown a marked effect on bone regeneration.[11,12] When OHC was compared in animals with the mineral component of the drug alone (hydroxyapatite, containing calcium and phosphorus) or with calcium carbonate (CC), observations from histological sections of the bone examined with a fluorescent microscope indicated improved bone formation in the OHC group.[11,12] Other studies suggest that OHC stimulates bone metabolism,[13] particularly when osteoblastic activity is reduced, by stimulating the differentiation, activity, and proliferation of osteoblasts by means of ossein.[14]

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Some preliminary studies have suggested that OHC is considerably more successful at maintaining BMD than CC.[15-19] To test the hypothesis that OHC is more effective in maintaining BMD than CC, we performed a systematic review of existing trials and carried out a meta-analysis to evaluate the effect of OHC on BMD in comparison with CC in participants with osteoporosis or at risk of having it.

METHODS

Study participants and interventions

Participants included were women and men older than 18 years with a clinical diagnosis of osteopenia or osteoporosis or with risk factors for osteoporosis. Participants with gastrointestinal problems that could restrict absorption of the study medications were excluded.

One tablet of OHC (Osteopor/Ossopan/Osteogenon, 830 mg of OHC per tablet; Pierre Fabre Médicament, Castres, France) contains calcium (178 mg), phosphorus (82 mg), and proteins associated with bone metabolism (osteocalcine: 5.8 μg; type I collagen: 216 mg; insulin growth factor type I: 168 ng; insulin growth factor type II: 84 ng; transforming growth factor-β: 21 ng).

In the systematic review we aimed to identify trials lasting at least 1 year that compared OHC and CC for the treatment or prevention of osteoporosis or osteopenia. Only trials in which OHC and CC were taken orally, with or without vitamin D, were included. Dose treatment was defined by the trials selected.

Systematic review and study selection

To identify studies of interest for the review, the following search terms were used: hydroxyapatite or ossein-hydroxyapatite compound or Osteopor or OHC or Ossopan or Osteogenon and osteoporosis or osteopenia and randomized clinical trial. The search was conducted in MEDLINE (October 1996-November 2008), EMBASE (1974-November 2008), and the Cochrane Controlled Trials Register and was limited to English- and Spanish-language publications and to studies in humans. Authors of some of the articles identified[15-17,20] and the pharmaceutical company that markets OHC were contacted to obtain additional information on some trials. The reference lists of the systematic reviews, meta-analyses, and randomized controlled trials (RCTs) identified were handsearched to locate additional RCTs.

RCTs that compared the efficacy of OHC and CC could be centered on either prevention or treatment of bone loss or both. Only clinical trials that used densitometry to measure percent change in trabecular bone (vertebra or distal radius) were included. Trials that used radiogrammetry were excluded.

Two reviewers (M.J.M.Z. and J.M.) independently evaluated the eligibility of the trials for inclusion in the meta-analysis. When disagreement occurred, the decision to include or exclude the trial was taken by consensus with two further reviewers (L.P.E. and M.C.R.). All authors participated in the analysis and interpretation of the data, reviewed the article, and approved the final version.

One reviewer (M.J.M.Z.) extracted data from the articles included using a standard protocol agreed by the study team. Information on participant characteristics, treatment, and outcome measures was collected. The primary endpoint was percent change in BMD from baseline.

Study evaluation

The quality of the trials identified was evaluated in terms of randomization, treatment blinding, dropouts, and analysis (per protocol or intention to treat). This information was used

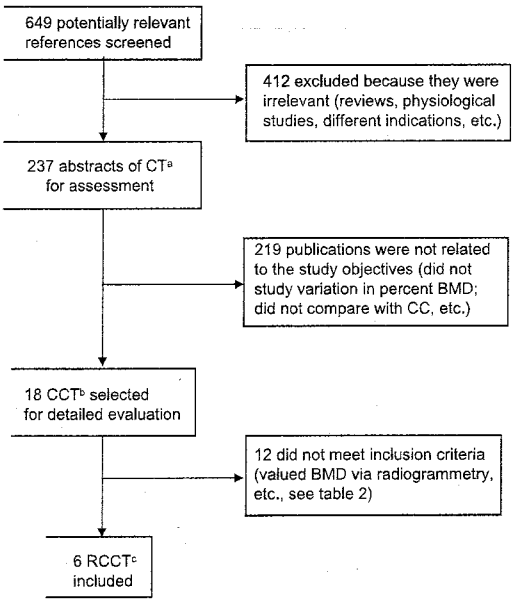

FIG. 1. Flow chart of trial selecting process. BMD, bone mineral density.

TABLE 1. *Characteristics of the included clinical trials*

Trial	Participants	Interventions [n participants by intervention]	Variables evaluated	Place of measurement	Measuring apparatus	Quality
Rüegsegger et al[18]	40 women with osteoporosis and nontraumatic vertebral fracture; age range: 58-78 y	(1) OHC 6.64 g/d (equivalent to 1,400 mg of calcium) tablets orally, 20 mo [20] (2) CC (equivalent to 1,400 mg calcium)/d tablets orally, 20 mo [20]	Percent change in trabecular and cortical BMD	Radius and tibia	Quantitative CT (pQCT)	+ Jadad 3
Chevalley et al[25]	A. 93 participants (11 men) without hip fracture and with a prevalence of vertebral fracture/participant of 0.9; age range: 62-87 y	A. (1) OHC 3.32 g/d orally, 18 mo [31]	Percent change in BMD	Lumbar spine	DPA (Norland 2600)	+ Jadad 3
		(2) CC 2,000 mg/d (or 800 mg of calcium element/d) orally, 18 mo [31] (3) Placebo [31] All groups received a single oral dose of vitamin D_3 (300,000 IU)	Incidence of new vertebral fracture	Femoral neck Femoral shaft		
	B. 63 participants (8 men) with a recent hip fracture; age range: 60-90 y	B. (1) OHC 3.32 g/d orally, 18 mo [31] (2) CC 2,000 mg/d orally, 18 mo [32]				
Lorenc et al[17]	125 postmenopausal women with osteopenia or osteoporosis (3); mean age: 65 y; age range: 55-83 y	(1) OHC 6.64 g/d tablets orally, 2 y [42] (2) OHC 6.4 g/d sachets (powder) orally, 2 y [42] (3) CC 1.5 g of calcium element/d orally, 2 y [41] All groups received vitamin D_3 (600 IU/d)	Percent change in BMD	L2-L4 Femoral head Trochanter Ward's triangle Radius Calcaneum	DXA (Lunar DPX-L system) Quantitative CT (pQCT) Ultrasound	± Jadad 2
Castelo-Branco et al[15]	60 postmenopausal women with normal BMD; mean age (OHC and CC groups): 54-53 y	(1) OHC 3.32 g/d orally, 2 y [19]	BMD	L2-L4	DXA (Lunar DPX-L system; Lunar Radiation Corporation, Madison, WI)	± Jadad 2
		(2) CC 2.5 g/d orally, 2 y [21] (3) No treatment [20]	Percent change in BMD			
Castelo-Branco et al[16]	118 surgically postmenopausal women with normal BMD; mean age (OHC and CC groups): 46-48 y	(1) OHC 3.32 g/d orally, 1 y [28]	BMD	L2-L4	DXA (Lunar DPX-L system; Lunar Radiation Corporation)	± Jadad 1
		(2) CC 2.5 g/d orally, 1 y [30] (3) 17β-estradiol 50 μg/d transdermal patch [28] (4) Combination of OHC (3.32 g/d orally, 1 y) + 17β-estradiol (50 μg/d transdermal patch) [32]	Percent change in BMD			
Ciria et al[20]	115 women with osteoporosis without evident fracture, older than 65 y; mean (±SD) age: 73 (±5) y	(1) OHC 3.32 g/d orally, 3 y [55] (2) CC 2.5 g/d orally, 3 y [60] All groups received vitamin D3 (400 IU/d)	BMD	Lumbar spine and femoral head	DXA (Hologic QDR 1000; Hologic Inc., Waltham, MA)	± Jadad 1

OHC, ossein-hydroxyapatite complex; CC, calcium carbonate; BMD, bone mineral density; CT, computed tomography; pQCT, peripheral quantitative computed tomography; DPA, dual-photon absorptiometry; DXA, dual-energy x-ray absorptiometry.

TABLE 2. *Characteristics of excluded clinical trials*

Trial/Year published	Reasons for exclusion
Epstein et al[19]	Evaluation of the metacarpal via radiogrammetry
Fernández-Pareja et al[26]	No data on percent change in BMD
Tovey et al[27]	Gastrectomized participants with poor gastrointestinal absorption; very high doses used
Khadzhiev et al[28]	No control group; evaluated pain and dental state; Bulgarian language
Pines et al[29]	Evaluation of the metacarpal via radiogrammetry
Stěpán et al[30]	Evaluation of the metacarpal via radiogrammetry
Stellon et al[31]	No data on percent change in BMD
Albertazzi et al[32]	Six-month treatment duration. The quantitative composition of the main active ingredients in OHC was different to that used in the trials included because it was obtained from a different source.
Lugli et al[33]	Controlled CT with placebo, in which lumbar pain was evaluated in participants with senile osteoporosis
Hegg et al[34]	No data on percent change; Portuguese language
Ringe and Keller[35]	RCT comparing OHC with no treatment; heparin treatment; 6-mo treatment duration
Pelayo et al[36]	Evaluation of the metacarpal using ultrasound

BMD, bone mineral density; CT, clinical trials; RCT, randomized controlled trial.

to classify the trials in one of the Scottish Intercollegiate Guidelines Network[21] categories, as follows: ++ (high quality), + (intermediate quality), and − (low quality). The scale of Jadad et al[22] was also used to rate trial quality. It provides a rating from 0 (low quality) to 5 (high quality) based on the quality of randomization, whether the trial is double-blinded, dropouts, and intervention masking.

Statistical methods

Data were analyzed using Revman 4.2.[23] Before the global estimate of effect was obtained, an analysis was carried out to test for heterogeneity. Heterogeneity was assumed when $P < 0.10$.

The analysis of efficacy was performed using a random-effect model[24] because the trials included had evaluated BMD in different bones, using different methods of densitometry, and the intervention had been assessed in different levels of bone loss. The overall effect was calculated using the weighted mean difference (WMD). Values greater than 0 (including 95% CI) indicated that OHC was more effective, and negative values favored CC. A value of zero meant that treatments were equivalent in terms of efficacy. We also performed a secondary analysis using a fixed effects model.

Two trials[15,16] provided the mean but not the SD of the percent change in BMD, and they did not include data that allowed us to calculate the SD. For these trials, we calculated the mean and SD using the WMD and its CIs obtained by combining data from studies that did report these data.[17,18,20,25] The maximal value, which is a more conservative estimate of the calculated mean and SD, was used to provide the missing data.

To verify the consistency of the results from the main analysis, a sensitivity analysis was carried out in which studies without full data[15,16] were excluded. We also performed a sensitivity analysis to evaluate whether the administration of vitamin D affected the results.

RESULTS

Description of the trials

From a total of 649 publications identified, 18 controlled clinical trials were selected for further review (Fig. 1). Additional information that was not in the original publications was obtained for three of these publications.[15,17,20] After evaluating the full text of the selected trials, six randomized controlled clinical trials were eventually included in the meta-analysis. All of these compared OHC with CC (Table 1). Because one of the articles[21] reported the results from two different groups of participants (with and without hip fracture), the data were included as two separate groups. Twelve trials were excluded[19,26–36] for the reasons given in Table 2.

Study quality was acceptable in two trials[18,25] and slightly lower in the remaining four.[15–17,20] All were randomized and controlled. Other metabolic bone disorders, thyroid dysfunction, and treatment with corticosteroids were common exclusion criteria for all the trials, whereas screening for renal insufficiency was reported in all but one.[18] Three of the trials reported the evaluation of baseline calcium consumption[15,17,25] and two provided information on smoking habits.[15,18] Initial levels of vitamin D were not tested in any of the trials, although it was administered in three of them.[17,20,25] One study[18] described the randomization process and treatment blinding. Some trials provided details of dropouts.[15,17,25]

TABLE 3. *Percent change in BMD in included trials*

Trials	Ossein-hydroxyapatite, % change (SD)	Calcium carbonate, % change (SD)
Castelo-Branco et al[15]: L2-L4	−0.40	−3.70
Castelo-Branco et al[16]: L2-L4	0.30	−1.10
Lorenc et al [17]: L2-L4	3.28 (4.95)	1.90 (6.91)
Rüegsegger et al[18]: Distal part of radius	−0.8 (0.5)	−1.8 (0.7)
Ciria et al[20]: L2-L4	−1.1 (5.5)	−2.3 (5.8)
Chevalley et al[25]: Participants without hip fracture, L2-L4	1.4 (1.1)[a]	1.9 (1.3)[a]
Chevalley et al[25]: Participants with recent hip fracture, L2-L4	5.0 (1.6)[a]	1.2 (1.7)[a]

BMD, bone mineral density.
[a]Mean ± SEM (in %).