Use of ossein–hydroxyapatite complex in the prevention of bone loss: a review

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ABSTRACT

Background and objective The ossein–hydroxyapatite complex (OHC) is a microcrystalline form of calcium which provides a number of additional minerals (magnesium, phosphorus, potassium, zinc), and proteins (osteocalcin, type I collagen, type I insulin growth factor I and II, transforming growth factor beta) associated with bone metabolism. The objective of this review is to examine the role of OHC in preventing bone loss in different conditions.

Material and methods A review of clinical trials assessing the relationship between OHC and bone loss was made using the following data sources: Medline (from 1966 to December 2013), the Cochrane Controlled Clinical Trials Register, Embase (up to December 2013), contact with companies marketing the supplements studied, and reference lists.

Results Different randomized, clinical trials and meta-analysis suggest that OHC is more effective than calcium supplements in maintaining bone mass in postmenopausal women and in different conditions related to bone loss. In addition, OHC improves pain symptoms and accelerates fracture consolidation in patients with osteopenia or osteoporosis.

Conclusion The ossein–hydroxyapatite complex is significantly more effective in preventing bone loss than calcium carbonate.

INTRODUCTION

Calcium and vitamin D are crucial for bone health and essential in the prevention and treatment of osteoporosis[1]. However, concerns have been raised about the risk–benefit ratio of the administration of total calcium and vitamin D in foods and supplements. The high intake of calcium supplements has been related in some[2,3], but not all studies[4–6] to an increased risk of cardiovascular events. On the other hand, several studies have shown that low levels of 25-hydroxyl vitamin D, the main circulating metabolite of vitamin D, are associated with an increased risk of cardiovascular events[7,8] and/or mortality by any cause[9,10]. However, high levels of vitamin D have also been implicated in increased mortality in women[11] but not in men[12]. Conversely, an adequate intake of calcium and vitamin D is needed to maintain bone health and prevent the risk of fracture[13].

The ossein–hydroxyapatite complex (OHC) has been used to prevent and treat primary and secondary osteoporosis, to regulate the balance of calcium and phosphorus in conditions such as pregnancy and lactation, or as adjunct therapy to accelerate the healing of bone fractures, among others, with an excellent safety profile[14–31]. [14,15,16]

OHC has shown greater bone regeneration than that observed with isolated hydroxyapatite or calcium salts[22,27]. This complex also modulates bone turnover, particularly in cases of reduced osteoblast activity by stimulating osteoblast differentiation, proliferation and activity through ossein[32–36] and decreasing bone resorption[37] (Table 1). All these OHC properties have been corroborated by randomized trials and

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REVIEW

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Table 1 Proposed mechanisms of action of the ossein–hydroxyapatite (OHC) compounds

Study	*Proposed mechanisms*
Reduction of bone resorption	
Chavassieux (1991)[32]	Crucial for bone mineralization (bone histomorphometry)
	Controls (no treatment): 45% increase in trabecular bone erosion surface, 60% reduction in osteoblast surface, 20% decrease in rate of bone formation
	No significant changes in OHC group
Castelo-Branco (2007)[33]	OHC decrease urinary calcium excretion
Lotinun (2013)[36]	Decreases bone resorption by delaying development of osteoclast precursors through TGF-β, osteocalcin, IGF-I, IGF-II and collagen type l
Lugli (1990)[37]	Significant reduction in urinary hydroxyproline excretion suggests decrease in bone resorption
Increasing bone formation	
Lorenc (1991)[18]	Required for bone mineralization (bone turnover markers):
	Bone formation markers: OHC decreases osteocalcin and PINP < CC; OHC increases PICP > CC
	Bone resorption markers: OHC decreases CTX > CC; NTX, pyridinoline and deoxypyridinoline decreased with OHC but increased with CC
Yang (2003)[35]	Stimulates bone formation by osteoblast differentiation and proliferation
Srimongkol (2005)[34]	Significant increase in PICP suggests an increase in bone formation

CC, calcium carbonate; TGF-β, transforming growth factor-β; IGF, insulin-like growth factor; PINP, N-terminal propeptide of type 1 procollagen; PICP, procollagen type 1 propeptide; CTX, carboxy-terminal collagen cross-links; NTX, N-terminal telopeptide

meta-analyses suggesting that OHC is clinically more effective in maintaining bone mineral density (BMD) than calcium supplements[15,16,38] (Tables 2–4).

In this review, an attempt is made to summarize the major published reports on the effectiveness of OHC in bone in different clinical situations as well as to evaluate the utility of OHC for bone health in women and emphasize the points that still need further clarification and additional research.

METHODS

Information sources

In January 2014, we searched Embase, Medline, and the Cochrane Library for all data up to and including December 2013 to identify potentially relevant publications. In order to maximize the number of publications meeting the selection criteria, the medical departments of companies marketing ossein–hydroxyapatite supplements were contacted to request publications that were not identified during the electronic search. Reference lists from studies initially selected and from existing reviews were also sought to identify any additional relevant studies not identified by the electronic searches.

Search strategy

To identify all the articles describing the use of the OHC in the treatment and prevention of bone loss, we designed the following search strategy including: osteoporosis or bone loss or bone fracture or BMD and hydroxyapatite or ossein–hydroxyapatite compound or Osteopor or Ossopan or Osteogenon and randomized, clinical trials. This strategy was adapted and applied to different Internet search engines, based on Medline and Cochrane Controlled Trials Register data. There were no language or date restrictions. Controlled and randomized studies evaluating the use of OHC in the treatment and prevention of osteoporosis were included.

Study selection

One reviewer (C.C.B.) independently evaluated the eligibility of the trials. Articles reviewed that did not establish the indication of administration, literature reviews or those whose purpose was not to demonstrate a therapeutic impact were not considered. In the final selection of articles, only those using diagnostic techniques currently recognized to diagnose systemic bone loss were included.

Eligibility criteria

Publications were included if the full text of the article was available. All types of clinical studies were included. Publications were included only if they contained information on the treatment administered together with the dose, duration and reason for treatment, participant characteristics, and study design and duration.

Data extraction

For each study included, one author extracted the data and a second author confirmed the data selected. Any potential discrepancies were resolved by consensus.

Table 2 Ossein–hydroxyapatite compounds (OHC) in the prevention of postmenopausal osteoporosis. Summary of the included clinical trials

Author	*Type of study*	*Follow-up*	*Sample*	*Treatment groups*	*Outcomes*	*Results*
Castelo-Branco[29]	controlled open study, prospective randomized	12 months	118 surgically menopausal women	1. HT ($n=28$) 2. OHC ($n=28$) 3. HT+ OHC ($n=32$) 4. No treatment control group ($n=30$)	change in spine BMD	+2.2% HT ($p<0.01$)* vs. +0.3% OHC vs. +4.7% HT + OHC ($p<0.01$)* vs. −1.1% control ($p<0.05$)* (intergroups, $p<0.01$)
Castelo-Branco[30]	controlled open study, prospective randomized	2 years	60 postmenopausal women	1. OHC ($n=19$) 2. Calcium carbonate ($n=21$) 3. No treatment ($n=20$)	change in spine BMD	1st year: −0.2% OHC vs. −1.0% CC vs. −3.5% control ($p<0.05$) 2nd year: −0.4% OHC vs. −3.7% CC vs. −5.6% control ($p<0.01$)
Castelo-Branco[19]	meta-analysis of RCTs	1–3 years	614 subjects in 6 RCTs	1. OHC 2. Calcium carbonate	change in spine BMD	+1.34% OHC vs. no changes in CC ($p<0.0001$)
Stepan[31]	controlled open study, prospective randomized	3 years	48 women with bilateral oophorectomy	1. OHC ($n=28$) 2. Control ($n=20$)	change in bone markers and bone density	Cortical BMD: −2.4% OHC vs. −6.94% control† Hydroxyproline: −30.3% OHC vs. −8.86% control† TRAP: −18.9% OHC vs. +2.1% control† Alkaline phosphatase: −30.1%OHC vs. −10.7% control†
Lorenc[32]	controlled open study, prospective randomized	12 months	125 post-menopausal women with osteopenia or osteoporosis	1. OHC ($n=84$) 2. Calcium carbonate ($n=41$)	change in BMD	+3.28 % OHC vs. −1.9% CC†
Fernández-Pareja[47]	retrospective observational study	4 years	237 post-menopausal women	1. OHC ($n=112$) 2. Control ($n=125$)	change in spine BMD	+3.2% OHC vs. −7.3% control‡

CC, calcium carbonate; HT, hormone therapy at menopause; BMD, bone mineral density; RCT, randomized, controlled trial; TRAP, tartrate resistant acid phosphatase

*, Changes vs. baseline; †, $p<0.01$; ‡, $p<0.0001$

RESULTS

After crossing-clearing the reference lists, a total of 326 studies relating to OHC and bone were identified. Of these, 38 were considered selectable and were allocated to one of the following topics according to the objective of the study for further review: OHC and bone metabolism, prevention of postmenopausal osteoporosis, treatment of postmenopausal osteoporosis, treatment and prevention of secondary osteoporosis, treatment and healing fractures, and OHC use during pregnancy.

The usefulness of OHC in different pathologies with decreased bone mass, which may determine both primary or secondary osteoporosis, was evaluated in the different studies summarized in Tables 2–4. Early in the 1970s, the first results of the clinical use of OHC in osteoporotic patients were published, demonstrating better calcium absorption than most other calcium salts[39]. Subsequent studies demonstrated that OHC was a safe and effective drug in the treatment of patients with metabolic bone diseases[17,40–45].

Table 3 Ossein–hydroxyapatite compounds (OHC) in the treatment of postmenopausal osteoporosis and healing fractures

Author	*Type of study*	*Follow-up*	*Sample*	*Treatment groups*	*Outcomes*	*Results*
Ciria[34]	open, parallel groups, controlled, prospective randomized	2 years	115 subjects with senile osteoporosis	1. OHC ($n = 55$) 2. CC ($n = 65$)	BMD femoral neck, bone turnover markers: osteocalcin, TRAP	BMD: 2.5% OHC vs. 1.2% CC; osteocalcin: 1.86% OHC vs. 0.31% CC*; TRAP: − 2.3% OHC vs. − 1.1 CC
Pelayo[54]	open, parallel groups, controlled, prospective randomized	3 years	90 women with osteoporosis	1. RLX + OHC 2. RLX + CC	BMD by ultrasound measurement of ADSoS	ADSoS: − 18.72 m/s from baseline to year 3 in RLX + OHC group and − 63.64 m/s in RLX + CC group‡
Durance[23]	open, parallel groups, comparative, randomized, prospective	9 months	14 subjects with severe osteoporosis (vertebral fractures)	1. OHC tablets ($n = 7$) 2. OHC powder ($n = 7$)	bone turnover markers: calcium, phosphate, proteins, total hydroxyproline; Rx metacarpal thickness, cortical bone biopsies	Reduced back pain, increased serum calcium, increased X-ray metacarpal cortical thickness. Increased serum calcium and not significant changes in cortical thickness. No differences between groups
Ruegsegger[33]	randomized, placebo-controlled double-masked study	20 months	40 women with postmenopausal osteoporosis	1. OHC ($n = 20$) 2. CC ($n = 20$)	radius and tibia BMD in 4-month intervals using pQCT	Loss of trabecular bone: 0.8 ± 0.5% OHC vs. 1.8 ± 0.7% CC group*. OHC more effective than CC in slowing peripheral trabecular bone loss in patients with manifest osteoporosis
Chevalley[55]	randomized, placebo-controlled double-masked study	18 months	93 healthy subjects; 63 subjects with recent hip fracture	1. OHC ($n = 31$) 2. CC ($n = 62$) 3. Placebo ($n = 31$) 4. OHC ($n = 31$) 5. CC ($n = 32$)	% changes in FS, FN and LS BMD	*Non-fractured women*: FS BMD (%): 0.6 ± 0.5 OHC + CC vs. -1.2 ± 0.7 placebo*. No difference between OHC and CC. FN BMD (%): 0.7 ± 0.8 OHC + CC vs. -1.7 ± 1.6 placebo (not significant) *Fractured patients*: LS BMD (%): 5.0 ± 1.6 OHC vs. 1.2 ± 1.7 CC; FN BMD (%): 5 ± 2.6 OHC vs. -0.9 ± 1.8 CC
Gyul'nazarova[48]	open, parallel groups, comparative, prospective	healing fractures, 6 months	42 osteoporotic patients with femoral or tibia fracture	1. OHC ($n = 15$) 2. CC + VIt D3 ($n = 12$) 3. Control ($n = 15$)	time to heal fracture	Femur: 285 control vs. 220 OHC* vs. 247.5 CC Tibia: 273 control vs. 180 OHC vs. 180 CC
Guptal[59]	open, parallel groups, comparative, prospective	healing fractures, 14 weeks	60 patients with long-bone fracture (30 undergone surgery, 30 closed reduction of fracture with immobilization)	A. *Non-operative group* 1. OHC ($n = 15$) 2. Placebo ($n = 15$) B. *Surgical group* 1. OHC ($n = 15$) 2. Placebo ($n = 15$)	time to heal fracture	Fracture consolidation: non-operative group: 11.3 weeks OHC vs. 14.03 weeks placebo†; surgical group: 10 weeks OHC vs. 14 weeks placebo
Mills[25]	randomized, placebo-controlled double-masked study	healing fractures, 10 months	85 patients with tibial shaft fracture ($26 \geq 55$ years, $59 < 55$ years)	A. *≥ 55 years* 1. OHC ($n = 13$) 2. Placebo ($n = 13$) B. *< 55 years* 1. OHC ($n = 29$) 2. Placebo ($n = 30$)	time to heal fracture	Fracture consolidation: ≥ 55 years: 11 weeks OHC vs. 14.2 weeks placebo*; < 55 years: 11.5 weeks OHC vs. 12.5 weeks placebo

CC, calcium carbonate; BMD, bone mineral density; TRAP, tartrate resistant acid phosphatase; ADSoS, amplitude-dependent speed of sound; pQCT, peripheral quantitative computed tomography; FS, femoral shaft; FN, femoral neck; LS, lumbar spine; RLX, raloxifene
*, $p < 0.05$; †, $p < 0.01$; ‡, $p = 0.006$

Table 4 Ossein–hydroxyapatite compounds (OHC) in the treatment and prevention of secondary osteoporosis

Author	*Type of study*	*Follow-up*	*Sample*	*Interventions*	*Outcomes*	*Results*
Nilsen[26]	controlled clinical trials		72 patients with rheumatoid arthritis	1st Group: OHC 2nd Group: Control		OHC group: decreased loss in size; increased BMD radio; decreased bone pain. Control group: decreased BMD radio; increased bone pain
Pines[37]	open RCT	1 year	40 subjects with respiratory disease treated with prednisone (dose $\geq$ 5 mg/day)	1. OHC ($n = 32$) 2. Control ($n = 8$)	mean cortical thickness; mean metacarpal index; back pain	mean cortical thickness and mean metacarpal index showed insignificant decreases (< 0.05 mm) in OHC group but much more marked decreases (0.03 mm) in control group. OHC group showed significant ($p < 0.001$) reduction in pain during trial, almost to point of its disappearance. Control group showed a back pain severity increase during trial in 3 patients and was unchanged in 4th
Stellon[38]	open RCT	2 years	36 corticosteroid-treated patients with chronic hepatitis	1. OHC ($n = 18$) 2. Control ($n = 18$)	Changes in: BMD radius; mean metacarpal index; TBV	BMD radius: 0% OHC vs. 4.06% Control*; mean metacarpal index: − 22.2% OHC vs. − 38.8% control†; TBV: +9.13% OHC vs. − 4.06% Control‡
Epstein[24]	open RCT	14 months	64 postmenopausal women with primary biliary cirrhosis	1. control (C, no supplements) 2. OHC 3. Calcium gluconate (CG) All patients received parenteral vitamin D2 (100 000 IU monthly)	changes in metacarpal cortical thickness; T, M, CT, CA, PCA	% ΔT − 0.8 C vs. 1.3 OHC† vs. − 0.2 CG; % ΔM + 4.2 C vs. − 2.9 OHC† vs. − 0.5 CG; % ΔCT − 5.5 C vs. 6.1 OHC† vs. 1.5 CG; % ΔCA − 4.9 C vs. 5.6 OHC† vs. 0 CG; Δ PCA% − 2.05 $\pm$ 0.62 C vs. +2.19 $\pm$ 0.64 OHC† vs. + 0.37 $\pm$ 0.47 CG
Varga[48]	Open, parallel groups, comparative, prospective	Healing fractures, 6 months	28 osteoporotic premenopausal women (13 rheumatoid arthritis, 15 chronic renal failure)	1. OHC ($n = 15$) (7 rheumatoid arthritis, 8 chronic renal failure) 2. Control ($n = 13$) (6 rheumatoid arthritis, 7 chronic renal failure)	Pain relief (VAS); time to heal fracture	*Fracture consolidation*: 26 days OHC vs. 32 days control† *Pain relief*: VAS basal 80 mm to VAS 20 mm; 21 days OHC vs. 35 days control†

CC, calcium carbonate; BMD, bone mineral density; RCT, randomized, controlled trial; TBV, trabecular bone volume; T, total metacarpal width; M, medullary cavity width; CT, cortical thickness; CA, cortical area; PCA, % cortical area; VAS, visual analog scale
*, $p < 0.005$); †, $p < 0.01$; ‡, $p < 0.025$

OHC in the prevention of postmenopausal osteoporosis

Castelo-Branco and colleagues[15] evaluated the effects of OHC on bone loss in healthy women receiving hormone therapy (HT) for climacteric complaints. The group receiving HT plus adjuvant OHC showed a greater increase in bone mineral content than those who only received HT, and the effect of OHC was greater than that observed in women on calcium carbonate (Table 2). In a subsequent study, the same authors assessed the effect of OHC in postmenopausal women who did not wish to take HT, demonstrating that continuous administration of OHC was more effective in preventing bone loss in postmenopausal women than calcium carbonate[16,46] (Table 2).

The use of OHC in the prevention of postmenopausal bone loss has also been studied in women with surgically induced menopause. In a series of 48 patients with prior bilateral oophorectomy (1–5 years), Stěpán and colleagues[17] found that the administration of OHC led to a reduction in the loss of BMD and biochemical markers of bone turnover (Table 2). Fernández-Pareja and colleagues, in a retrospective study, analyzed 237 postmenopausal women and found similar results[47].

Another comparative study involving osteopenic women was performed by Lorenc and colleagues[18] who compared the efficacy of OHC versus calcium carbonate in natural and surgically induced menopausal women older than 55 years with more than 5 years since the beginning of menopause. These authors observed a significant reduction of bone resorption in the OHC group.

OHC in the treatment of postmenopausal osteoporosis

Some evidence suggests that the organic component of OHC plays an important role in bone response in osteoporotic patients. The formulations that include ossein–hydroxyapatite show a significantly greater effect in bone than those with only a pure mineral supplement. In patients with severe osteoporosis, an increase has been observed in metacarpal and phalangeal bone density as well as a significantly higher decrease of pain than that observed with calcium[14,48] (Table 3).

This superior efficacy has also been observed in patients who already have osteoporotic vertebral[19,49] and hip[49] fractures. In a comparative study, OHC was more effective in preventing the loss of trabecular bone in patients with osteoporosis and at least one vertebral fracture due to fragility than calcium carbonate[19]. Additionally, the lack of adverse events in this study suggests the possibility of safe long-term treatment (Table 3).

It is noteworthy that anabolic actions on bone have recently been attributed to OHC. Ciria-Recasens and colleagues[20] conducted a comparative study with calcium carbonate on bone metabolism in women with senile osteoporosis and detected a higher increase in BMD and higher levels of osteocalcin in the group receiving OHC (Table 3). Similarly, Stamp and colleagues[21] suggested that the intake of sodium fluoride with OHC stimulates osteoblasts and induces new bone formation, increasing trabecular and osteoid bone volume (Table 3). Furthermore, the association of sodium fluoride with hydroxyapatite provides better absorption of calcium[50].

OHC in the treatment and prevention of secondary osteoporosis

An emerging concern is the prevention of bone loss in patients with chronic diseases treated with corticosteroids. Nilsen and colleagues[39] showed that, after 1 year of treatment, patients with rheumatoid arthritis receiving OHC showed significantly less loss of height and bone density at the radius and that bone pain also significantly improved (Table 4). Similarly, Varga and colleagues[51] found, in patients with rheumatoid arthritis and chronic renal failure treated with OHC, an analgesic effect and an improvement of well-being.

OHC has also been studied in other situations requiring chronic treatment with corticosteroids such as chronic obstructive pulmonary disease or autoimmune processes. Pines and colleagues[52] showed an increase in bone mineralization, a decrease in the progression of osteoporosis and a great reduction in skeletal pain in asthmatic patients with corticosteroid-induced osteoporosis receiving OHC (Table 4). This study demonstrated the excellent tolerability and safety of the drug.

OHC has been also administered in patients with autoimmune chronic active hepatitis undergoing corticosteroid therapy for long periods of time who developed corticosteroid-induced osteoporosis. In a group of 36 patients with corticosteroid-induced osteoporosis, Stellon and colleagues[53] showed that bone pain, plasma calcium and creatinine values decreased in the treated group and, contrary to what was observed in the control group, new vertebral fractures were not detected in the group receiving OHC (Table 4).

The role that cortical bone may play in bone quality and fracture risk is increasingly considered. Pathological cortical bone resorption is characteristic of malabsorption syndromes, chronic renal tubular acidosis, physical inactivity and primary biliary cirrhosis. In this way, Epstein and colleagues[43] demonstrated a positive effect of OHC in the prevention of cortical bone thinning in postmenopausal women with primary biliary cirrhosis. These authors also showed that vitamin D alone did not prevent the loss of cortical bone, and that the absorption of calcium was greater when OHC was administered instead of calcium carbonate. An additional advantage of OHC in situations with salt retention such as cirrhosis is the low sodium content of this complex compared to other calcium salts[43]. The effects of OHC on cortical bone are not related to the stimulation of bone formation but rather to a reduction in bone resorption. However, the exact mechanism of action is unknown[32,43].

OHC has also been studied in congenital defects of bone formation. Dent and Davies[40] evaluated the effect of the combination of OHC microcrystals and dihydrotachysterol in patients with imperfect osteogenesis. The positive calcium

balance observed was probably related to a better mineral absorption because of the presence of amino acids such as proline in the composition of OHC (Table 4).

OHC in the treatment and healing of fractures

Bone fractures are one of the most common causes of prolonged disability and loss of work for young people and of mortality in older patients[22]. Fracture healing inevitably takes time, and therefore the speed of healing and functional recovery are of great clinical and economic importance[22].

It is well known that the bone matrix contains substances that may regulate bone formation *in vitro* by controlling precursors of mitosis and stimulating osteoblastic activity[23], and experimental studies have shown that treatment with OHC results in accelerated fracture healing. However, this beneficial effect of OHC on the healing process of bone is lost when the organic components of the compound are destroyed or when OHC is replaced by pure calcium carbonate[22]. These data strongly suggest that the organic components of OHC have osteogenic effects.

New indications for the use of OHC in trauma lesions have recently been suggested, particularly in the treatment of severe skeletal lesions[24–26]. OHC has been demonstrated to reduce the rate of bone resorption and to stimulate ossification[24–27,51]. The administration of OHC as monotherapy in patients with both single and multiple bone fractures has shown a 1–4-week reduction in the time needed to heal fractures by stimulating callus formation and thereby accelerating consolidation and clinical improvement[24,25,28,44,51,54]. Finally, the use of OHC in patients with bone fractures and complications in regenerative osteogenesis has been associated with pain relief and the activation of anabolic processes that result in an increase in bone mass[24,29,30].

Use of OHC during pregnancy

OHC has also been used in pregnant women, proving to be effective in different complaints and safe[31,45,55–57]. In one study, OHC was given to 170 women with abdominal, pelvic, back and lumbosacral pain, paresthesias, alopecia, onychorrhexis and odontopathies throughout the pregnancy and postpartum period[31]. Most of the women receiving OHC showed a reduction or elimination of bone pain, with no further alopecia and onychorrhexis.

OHC was used in another study[45] for a period of 1 month in 20 pregnant women at 28–40 weeks' gestation with pain syndrome in the long bones, lumbosacral region and disturbed dental status, with a considerable clinical improvement of pain syndrome and dental status at the end of the treatment.

Finally, an improvement in muscular complaints has been observed in up to 77% of patients with functional muscle disorders related to pregnancy[55]. The positive therapeutic effect, easy way of administration, its good tolerance and lack of side-effects make it convenient for treatment of disturbances in calcium–phosphorus balance in pregnant women.

CONCLUSIONS

OHC has been demonstrated to be useful in different clinical situations in which bone metabolism is compromised such as in primary and secondary osteoporosis and osteogenesis imperfecta, mineral deficiency and increased mineral requirements (pregnancy, lactation, elderly patients), and fractures in the elderly. Finally, it is of note that OHC has been shown to be more effective than calcium carbonate in maintaining bone mineral density in postmenopausal women and that, when used with other antiresorptive agents, treatment outcomes improve.

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References

1. Papaioannou A, Morin S, Cheung AM, *et al*. 2010 clinical practice guidelines for the diagnosis and management of osteoporosis in Canada: summary. *CMAJ* 2010;182:1864–73
2. Bolland MJ, Barber PA, Doughty RN, *et al*. Vascular events in healthy older women receiving calcium supplementation: randomised controlled trial. *BMJ* 2008;336:262–6
3. Pentti K, Tuppurainen MT, Honkanen R, *et al*. Use of calcium supplements and the risk of coronary heart disease in 52–62-year-old women: The Kuopio Osteoporosis Risk Factor and Prevention Study. *Maturitas* 2009;63:73–8
4. Wang TKM, Bolland MJ, van Pelt NC, *et al*. Relationships between vascular calcification, calcium metabolism, bone density, and fractures. *J Bone Miner Res* 2010;25:2777–85
5. Manson JE, Allison MA, Carr JJ, *et al*. Calcium/vitamin D supplementation and coronary artery calcification in the Women's Health Initiative. *Menopause* 2010;17:683–91
6. Lewis JR, Calver J, Zhu K, Flicker L, Prince RL. Calcium supplementation and the risks of atherosclerotic vascular disease in older women: results of a 5-year RCT and a 4.5-year follow-up. *J Bone Miner Res* 2011;26:35–41
7. Wang TJ, Pencina MJ, Booth SL, *et al*. Vitamin D deficiency and risk of cardiovascular disease. *Circulation* 2008;117:503–11
8. Kendrick J, Targher G, Smits G, Chonchol M. 25-Hydroxyvitamin D deficiency is independently associated with cardiovascular disease in the Third National Health and Nutrition Examination Survey. *Atherosclerosis* 2009;205:255–60

9. Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008;168:1629–37
10. Dobnig H, Pilz S, Scharnagl H, *et al*. Independent association of low serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels with all-cause and cardiovascular mortality. *Arch Intern Med* 2008;168:1340–9
11. Ensrud KE, Ewing SK, Fredman L, *et al*. Circulating 25-hydroxyvitamin D levels and frailty status in older women. *J Clin Endocrinol Metab* 2010;95:5266–73
12. Ensrud KE, Blackwell TL, Cauley JA, *et al*. Circulating 25-hydroxyvitamin D levels and frailty in older men: the osteoporotic fractures in men study. *J Am Geriatr Soc* 2011;59:101–6
13. Ross AC, Manson JE, Abrams SA, *et al*. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *J Clin Endocrinol Metab* 2011;96:53–8
14. Durance R, Parsons V, Atkins C, Hamilton E, Davies C. Treatment of osteoporotic patients. A trial of calcium supplements (Ossopan) and ashed bone. *Clin Trial J* 1973;3:67–75
15. Castelo-Branco C, Martínez de Osaba MJ, Pons F, *et al*. Ossein-hydroxyapatite compounds for preventing postmenopausal bone loss. Coadjuvant use with hormone replacement therapy. *J Reprod Med* 1999;44:241–6
16. Castelo-Branco C, Pons F, Vicente JJ, Sanjuán A, Vanrell JA. Preventing postmenopausal bone loss with ossein-hydroxyapatite compounds. Results of a two-year, prospective trial. *J Reprod Med* 1999;44:601–5
17. Stěpán JJ, Pospíchal J, Presl J, Pacovský V. Prospective trial of ossein-hydroxyapatite compound in surgically induced postmenopausal women. *Bone* 1989;10:179–85
18. Lorenc RS, Hoszowski K Tlustochowicz W. No efficacy and safety of ossein-hydrohyapatite complex (OHC) 800 mg tablets and 3200 mg sachets versus calcium carbonate in osteoporotic post menopausal women. *Osteoporos Int* 1998;8(Suppl 3):102 (Abstr P319)
19. Rüegsegger P, Keller A, Dambacher MA. Comparison of the treatment effects of ossein-hydroxyapatite compound and calcium carbonate in osteoporotic females. *Osteoporos Int* 1995; 5:30–4
20. Ciria-Recasens M, Blanch-Rubió J, Coll-Batet M, *et al*. Comparison of the effects of ossein-hydroxyapatite complex and calcium carbonate on bone metabolism in women with senile osteoporosis: a randomized, open-label, parallel-group, controlled, prospective study. *Clin Drug Investig* 2011;31: 817–24
21. Stamp TCB, Jenkins MV, Walker PG MT. Treatment of osteoporosis with MCHC compound and sodium fluoride. *Int Congr Symp* 1983;9:287–90
22. Annefeld M, Caviezel R, Schacht E, Schicketanz KH. The influence of ossein-hydroxyapatite compound ('Ossopan') on the healing of a bone defect. *Curr Med Res Opin* 1986;10:241–50
23. Drivdahl RH, Howard GA, Baylink DJ. Extracts of bone contain a potent regulator of bone formation. *Biochim Biophys Acta* 1982;714:26–33
24. Kirilova IA, Fomichev NG, Podorozhnaya VT. New materials for bone grafting in view of current concepts. *Hir pozvonocnika* 2007;2:66–70
25. Rodionova SS, Kolondaev AF, Sokolov VA, Markov SA. Experience with the use of Osteogenon in traumatology and orthopedics. *Bull Traumatol Orthop* 2001;4:41–6
26. Faĭvishevskiĭ ML, Rodionova SS, Furtseva LN. [New calcium-containing product for complex treatment of osteoporosis]. *Vopr Pitan* 2001;70:32–5
27. Schmidt KH, Wörner UM, Buck HJ. Examination of new bone growth on aluminium oxide implant contact surfaces after oral administration of ossein-hydroxyapatite compound to rats. *Curr Med Res Opin* 1988;11:107–15
28. Bugaev D, Gorbunkov V. Diagnosis and treatment of fractures of the distal radius metaepiphysis in elderly and senile age. *Med New North Caucasus* 2013;1:108–12
29. Liu H, Peng H, Wu Y, *et al*. The promotion of bone regeneration by nanofibrous hydroxyapatite/chitosan scaffolds by effects on integrin-BMP/Smad signaling pathway in BMSCs. *Biomaterials* 2013;34:4404–17
30. Gul'nazarova SV, Kuznetsova OA. Ossein-hydroxyapatite complex in the treatment of patients with pseudoarthrosis of the femur and shin bones, complicated by systemic osteoporosis. *Bull Traumatol Orthop Priorov* 2006;2:21–4
31. Kunhardt Rasch J, Montoya Romero JJ, Diáz Loya FJ, Sosa de Martínez MC. [Measurement of calcium and phosphorus levels during pregnancy and the puerperium]. *Ginecol Obstet Mex* 1984;52:267–70
32. Chavassieux P, Pastoureau P, Boivin G, Delmas PD, Chapuy MC, Meunier PJ. Effects of ossein-hydroxyapatite compound on ewe bone remodeling: biochemical and histomorphometric study. *Clin Rheumatol* 1991;10:269–73
33. Castelo-Branco C, Haya-Palazuelos J, Cancelo-Hidalgo MJ. Menopause and osteoporosis: usefulness of ossein-hydroxyapatite complex. In Castelo-Branco C, Haya Palazuelos J, eds. *Osteoporosis and Menopause*. Madrid, Spain: Ed Medica Panamericana, 2007:217–25
34. Srimongkol T, Bunyaratavej N. Clinical study of efficacy of hydroxyapatite. *J Med Assoc Thai* 2005;88(Suppl 5):S24–6
35. Yang X, Tare RS, Partridge KA, *et al*. Induction of human osteoprogenitor chemotaxis, proliferation, differentiation, and bone formation by osteoblast stimulating factor-1/pleiotrophin: osteoconductive biomimetic scaffolds for tissue engineering. *J Bone Miner Res* 2003;18:47–57
36. Lotinun S, Kiviranta R, Matsubara T, *et al*. Osteoclast-specific cathepsin K deletion stimulates S1P-dependent bone formation. *J Clin Invest* 2013;123:666–81
37. Lugli R, Bruneti G, Salvioli G. Effect of ossein-hydroxyapatite compound on back pain in the elderly. Results of a placebo-controlled trial. *Clin Trials J* 1990;27:141–8
38. Castelo-Branco C, Ciria-Recasens M, Cancelo-Hidalgo MJ, *et al*. Efficacy of ossein-hydroxyapatite complex compared with calcium carbonate to prevent bone loss: a meta-analysis. *Menopause* 2009;16:984–91
39. Nilsen KH, Jayson MI, Dixon AS. Microcrystalline calcium hydroxyapatite compound in corticosteroid-treated rheumatoid patients: a controlled study. *Br Med J* 1978;2:1124
40. Dent CE, Davies IJ. Calcium metabolism in bone disease: effects of treatment with microcrystalline calcium hydroxyapatite compound and dihydrotachysterol. *J R Soc Med* 1980;73:780–5
41. Brenton D, Dent C. Idiopathic juvenile osteoporosis. In Bickel H, Stern J, eds. *Inborn Errors of Calcium and Bone Metabolism*. Lancaster, UK: MTP, 1976:222–38
42. Wagner JR. A 3 ½-year clinical evaluation of resorbable hydroxylapatite OsteoGen (HA Resorb) used for sinus lift augmentations in conjunction with the insertion of endosseous implants. *J Oral Implantol* 1991;17:152–64
43. Epstein O, Kato Y, Dick R, Sherlock S. Vitamin D, hydroxyapatite, and calcium gluconate in treatment of cortical bone thinning in postmenopausal women with primary biliary cirrhosis. *Am J Clin Nutr* 1982;36:426–30
44. Mills TJ, Davis H, Broadhurst BW. The use of a whole bone extract in the treatment of fractures. *Manit Med Rev* 1965;45:92–6
45. Khadzhiev A, Rachev E, Katsarova M, Cherveniashki S. [The results of a clinical trial of the preparation Ossopan]. *Akusherstvo i Ginekol* 1990;29:85–7

46. Castelo-Branco C, Pons F, Vanrell J. Prevention of postmenopausal-related bone loss with ossein hydroxyapatite compound in healthy subjects who did not wish to use hormone replacement therapy: results of a two year prospective trial. *Osteoporos Int* 1998;8(Suppl 3):102 (Abstr P318)
47. Fernández-Pareja A, Hernández-Blanco E, Pérez-Maceda JM, Riera Rubio VJ, Palazuelos JH, Dalmau JM. Prevention of osteoporosis: four-year follow-up of a cohort of postmenopausal women treated with an ossein-hydroxyapatite compound. *Clin Drug Investig* 2007;27:227–32
48. Pelayo I, Haya J, De la Cruz JJ, *et al.* Raloxifene plus ossein-hydroxyapatite compound versus raloxifene plus calcium carbonate to control bone loss in postmenopausal women: a randomized trial. *Menopause* 2008;15:1132–8
49. Chevalley T, Rizzoli R, Nydegger V, *et al.* Effects of calcium supplements on femoral bone mineral density and vertebral fracture rate in vitamin-D-replete elderly patients. *Osteoporos Int* 1994;4:245–52.
50. Brazier M, Fardelonne P, Bellony R, Sebert JL, Desmet G. [Fluoride bioavailability from sodium fluoride alone or in association with different calcium salts]. *Eur J Drug Metab Pharmacokinet* 1991;Spec No 3:161–5
51. Varga OI, Vezikova NN, Marusenko IM, Kheĭfets LM. [Osteogenon in therapy of distal radial bone fractures in patients with secondary osteoporosis]. *Ter Arkh* 2007;79: 52–4
52. Pines A, Raafat H, Lynn AH, Whittington J. Clinical trial of microcrystalline hydroxyapatite compound ('Ossopan') in the prevention of osteoporosis due to corticosteroid therapy. *Curr Med Res Opin* 1984;8:734–42
53. Stellon A, Davies A, Webb A, Williams R. Microcrystalline hydroxyapatite compound in prevention of bone loss in corticosteroid-treated patients with chronic active hepatitis. *Postgrad Med J* 1985;61:791–6
54. Gupta S. Ossopan in the treatment of fracture of long bones. *Ind Med Gaz* 1981;9:312–14
55. Warnecke G. Experience with ossein-hydroxyapatite complex (Ossopan®) in musculoskeletal dísorders of pregnancy. *Zeit Artz Klin Prax* 1987;62:1862–3
56. Grall J, Arvis P, Mention J. Etude de l'activite d'un complexe d'hydroxyapatite microcristalline (CHMC) au cours de la grossesse. *Actual Thérapeutique* 1984;91:82–4
57. Morin P, Ameteau J, Paupardin C. Intérêt d'un extrait d'os total chez la femme enceinte. *Gaz Med* 1977;84:2839–43