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Postmenopausal Osteoporosis and Osteopenia Management with a Combination of Once-Monthly Oral Ibandronate and Cholecalciferol—A Systematic Review

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Abstract

Postmenopausal osteoporosis and osteopenia are chronic and uncurable conditions that invariably lead to an increased risk of vertebral, hip, and femoral neck fracture if left untreated. Clinical guidelines establish, in general, pharmacological combinations allied to lifestyle changes as the mainstay of their management, and also increasing bone marrow density, lowering fracture risk, and improving quality of life are their main therapeutic goals. The objective of this systematic review was to analyze the available data in the scientific medical literature regarding the role of the ibandronate and cholecalciferol combination in postmenopausal osteoporosis and osteopenia management. Based on our results, we concluded that the above combination is safe and feasible for the clinical control of both conditions.

Keywords

Ibandronate, Cholecalciferol, Postmenopausal Osteoporosis, Postmenopausal Osteopenia, Systematic Review

1. Introduction

Postmenopausal osteoporosis imposes an enormous human and economic burden on healthcare systems all over the world. Bound to compromise all women after their reproductive years (even though in varying degrees), this condition drives huge efforts in all research levels at international, public administration, pharmaceuticals, and university settings to elucidate its natural history, as well as finding either novel or repositioned therapeutic modalities. Ibandronate is a substance of the bisphosphonates class, able to decrease osteoclast activity, reduce bone crystalized inorganic mineral matrix solubility, and downregulate proosteoclasts signaling, with an overall effect of slowing down, preserving, or increasing bone mineral density (BMD) [1] [2] [3] [4] [5]. Cholecalciferol is the most widely used substance of the vitamin D class, universally indicated for postmenopausal osteoporosis and osteopenia prevention and treatment due to its ability to make calcium and phosphate available to the bone remodeling process. Assuming pharmacological combination therapy for postmenopausal osteoporosis management has a consensus status for most clinical situations, the association of ibandronate and cholecalciferol presents itself as a feasible resource for increasing patient adherence, as well as assuring therapeutic efficacy. Therefore, we aimed to retrieve through a systematic review of the available evidence in the scientific clinical literature detailing the safety and efficacy of the ibandronate and cholecalciferol combination in the setting of postmenopausal osteoporosis and osteopenia management. To the best of our knowledge, ours is the first initiative of performing a grouped analysis of previously published papers with the above combination.

2. Methodology—Primary Studies Search and Selection

The study was performed by two independent "searchers" (MS and LHS) who worked in parallel and blindly, both according to the following parameters: 1) epidemiological studies, observational studies, randomized clinical trials (RCT), non-RCT, systematic reviews and meta-analyses as study types; 2) no language or year of publication restrictions; 3) the names of the authors of the primary studies were not regarded (even though personal consulting was permissible); 4) the following sources were scrutinized, with respective parameters:

- Pubmed: "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text
- *Literatura Latino-Americana e do Caribe em Ciências da Saúde* (LILACS): "*ibandronato*" in the title and "*colecalciferol*" or "*vitamina D*" anywhere in the text
- Google Scholar: 1) "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text; 2) up to three search pages
- Networked Digital Library of Theses and Dissertations (NDLTD): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text
- *Biblioteca Digital Brasileira de Teses e Dissertações* (BBTD): "*ibandronato*"

in the title and "*colecalciferol*" or "*vitamina D*" anywhere in the text

- World Congress on Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (WCOOMD): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text (Google and Pubmed platforms)
- European Congress on Osteoporosis and Osteoarthritis (ECOO): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text (Google and Pubmed platforms)
- National Osteoporosis Foundation (NOF): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text (Google and Pubmed platforms)
- American Academy of Orthopaedic Surgeons (AAOS): "ibandronate" in the title and "cholecalciferol" or "vitamin D" anywhere in the text (Google e Pubmed platforms)
- Bibliographic references from the selected publications

Support literature, such as textbooks, basic science papers, and pharmacological compendiums, was consulted when deemed necessary (not accounted for systematic review purposes). The studies search was performed according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [6]. Flowchart is depicted in **Figure 1**.

Results of the "searchers" were crossed by a reviewer for validation, who reported no conflicts between the body of findings of the former two. Studies were selected through respective titles and abstracts, according to the following parameters of interest: BMD maintenance at medium and long term, bone fracture risk reduction, comparison with other bisphosphonates, influence on patients' quality of life, effects on blood levels of markers linked to bone metabolism, influence on bone tissue and tolerability. Text search was extended from the title/abstract to the body of the text when searchers felt necessary. No personal contact with the studies' authors was necessary. A comprehensive literature on the general pharmacology of ibandronate and cholecalciferol was also retrieved.

3. Postmenopausal Osteoporosis

3.1. Definition and Pathophysiology

Osteoporosis is a bone degenerative condition characterized by low cortical and/or trabecular density of the hip, vertebrae, femoral neck, and/or distal forearm, expressed as a T-score ≤2.5 standard deviations (SD) as measured by bone densitometry (DXA). Postmenopausal osteoporosis occurs in the context of the physiological lowering of estrogen secretion, typical of this phase of life (biomechanical defects and aging are co-mechanisms) [1] [3]. Bone remodeling is accelerated, leading to a net loss of bone tissue with each cycle. Since trabecular bone is more susceptible to this phenomenon than cortical bone, one can assume that osteoporosis might be more common in bones where the former prevails such as the hip, vertebrae, and femoral neck. Subsequent deterioration of bone architecture and strength loss predispose either to fracture due to trauma

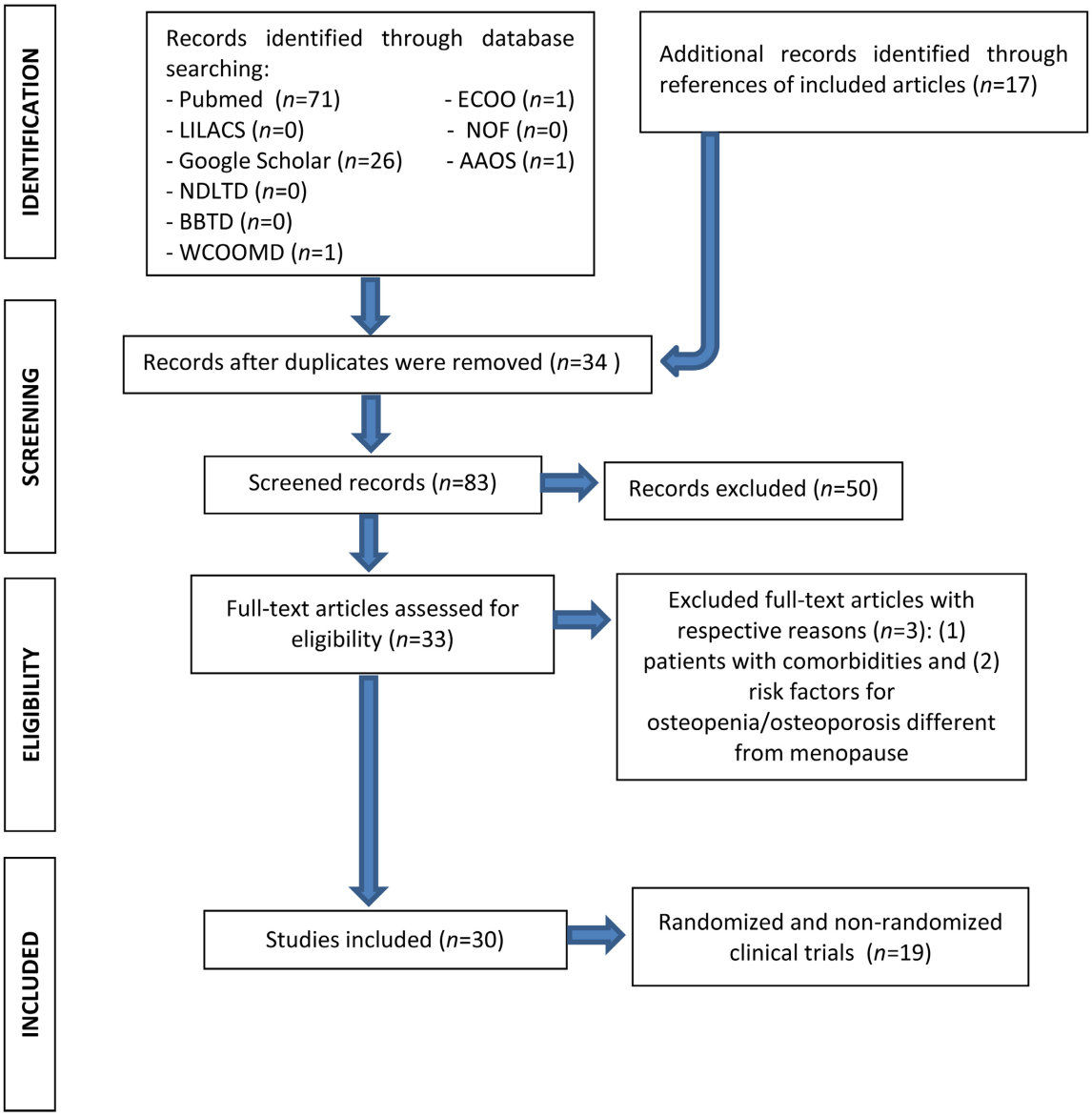

Figure 1. Diagram for study selection as applied in the current systematic review.

of lesser magnitude or to atypical fractures. It is a subclinical condition until complicated with bone fracture [2] [4].

3.2. Epidemiology

Women in their 6th decade of life present a 40% risk of experiencing an osteoporotic fracture, with the vertebrae being the most commonly affected bones. The latter type of fracture is associated with the following rates: 1) two-thirds occur in women >75 years of age, 2) there is a 5-fold increased risk for additional vertebral fractures, and 3) there is 2- to 3-fold increased risk for hip, proximal femur or distal forearm fractures [3]. Despite their greater frequency, vertebral fractures can be asymptomatic [1] [7]. Hip fractures result in greater morbidity, mortality, and costs than all other osteoporotic fracture types combined, as 60%

of patients do not regain their pre-fracture independence [1] [3].

3.3. Radiological Diagnosis

DXA of the total hip, femoral neck, or lumbar spine is considered the gold standard for osteoporosis diagnosis, therapeutic follow-up, and therapeutic change assessment [3]. Known limitations of this technique are:

- Poor precision for changes of <3% to 6% and <2% to 4% in BMD of hip and spine, respectively [3].
- Measurement of crystalized inorganic mineral matrix density, disregarding osseous connective tissue (collagen fibers, osteocalcin, and other non-collagen proteins).

Based on this limitation, one can suppose that a T-score increase might not forcibly reflect a clinically significant bone microarchitectural improvement. In fact, even when BMD measurements have not significantly increased, fracture risk can decrease disproportionately, suggesting that other factors of bone strength different than the crystalized inorganic mineral matrix might play a role [3] [4].

3.4. Laboratory Diagnosis

Even though biochemical markers of bone turnover (s-CTx, urinary N-telopeptide, propeptide type 1 procollagen, bone-specific alkaline phosphatase, and osteocalcin) are not recommended for postmenopausal osteoporosis diagnosis, they can be useful in predicting rapidity of bone loss, as a tool for estimating the magnitude of BMD post-therapeutic increases and to point out the timing for medication resumption during a "bisphosphonates holiday" (see further) [3].

3.5. Pharmacological Prophylaxis

Indications for postmenopausal osteoporosis prophylaxis are [3]:

- primary fracture prevention: 1) T-score ≤2.5 at the femoral neck and total hip and 2) osteopenia (T-score between −1.0 and −2.5) at the femoral neck or hip *plus* either 10-year hip fracture risk ≥3% or a 10-year major osteoporosis-related fracture risk ≥20% (based on FRAX model*).
- secondary fracture prevention: 1) fracture of hip or vertebra (regardless of BMD) and 2) fracture of the proximal humerus, pelvis, or distal forearm under a T-score between −1.0 and −2.5.

Therapeutic classes and drugs approved for the prevention and/or treatment of postmenopausal osteoporosis are bisphosphonates, selective estrogen-receptor modulators (e.g., raloxifene), human monoclonal antibodies to sclerotin (e.g., romosozumab), strontium ranelate, recombinant parathyroid hormone (PTH analogs) (e.g., teriparatide), tissue-selective estrogen complex, receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitors (denosumab), calcitonin

*FRAX model is an assessment tool for estimating 10-year bone fracture risk in treatment-naïve individuals, based on parameters such as a history of fractures, BMD, and parental history.

and estrogen therapy [1]. Parameters for the best modality choice are fracture prevention efficacy, site of optimal fracture prevention (spine vs. hip), and the onset of effect [3]. Assuming that postmenopausal osteoporosis is an uncurable and inexorably evolving condition, treatment can never be stopped (even though "holidays" can be considered) and the achieved benefits can only be maintained as long as the therapy endures [3].

4. Bisphosphonates Class

4.1. Pharmacology

Bisphosphonates represent a class of drugs that increases bone strength by inhibiting tissue resorption during its physiological remodeling process. They are mainly indicated as first-line therapy for postmenopausal osteoporosis prevention and management [4]. The following mechanisms of action are described for this class of drugs [1] [2] [3] [4] [5].

- inhibition of osteocyte farnesyl diphosphate synthase (mevalonate pathway).

Osteocyte enzyme farnesyl diphosphate synthase (FDS) yields farnesyl pyrophosphate, which promotes prenylation (addition of hydrophobic molecules) of small GTPase signaling proteins, a phenomenon involved in osteoclast activation. By inhibiting FDS, bisphosphonates stop the prenylation of these GTPase signaling proteins, either preventing osteoclasts activation or leading to cell apoptosis [8].

- hydroxyapatite crystals' solubility decrease.

Bisphosphonates are chemically composed of two phosphate groups that allow binding to hydroxyapatite crystals composing the crystalized inorganic mineral matrix, decreasing the solubility of the latter and slowing down bone resorption.

- proosteoclasts signaling downregulation.

Reduced hydroxyapatite crystals solubility, as described above, prevents osteocyte cytokines from reaching proosteoclasts, stopping their differentiation into osteoclasts.

Bisphosphonates' nadir effect on osteoclast activity is expected to be attained within 3 months of therapy and will inevitably lead to inhibition of osteoblasts activation and therefore bone remodeling. Nevertheless, within 3 additional months, an equilibrium is expected to take place, leading to a net result of either BMD preservation or gain. After this term, a clinically significant reduction of fracture risk is expected to be reached [4]. Bisphosphonates take longer to bring BMD and fracture risk to baseline levels than non-bisphosphonates, but their effect stands longer after interruption (this characteristic can be advantageous during the so-called "bisphosphonates holiday") [3].

4.2. Safety

Bisphosphonates' immediate side effects are limited to the digestive system (esophageal irritation, dysphagia, and gastrointestinal symptoms) [4]. The drugs of this class are potentially nephrotoxic and therefore are contraindicated in pa-

tients with a glomerular filtration rate <30 mL/min. Inhibition of osteoclast activity caused by bisphosphonates is expected to lower calcium efflux to the blood, leading to one-week duration hypocalcemia, which is clinically unimportant in most cases. Nevertheless, bisphosphonates are contraindicated in patients with preexisting hypocalcemia or under other associated risky conditions, such as hypoparathyroidism [4] [5]. Prolonged suppression of bone resorption and its subsequent formation can lead to tissue microdamage accumulation and bone frailty [4].

Bisphosphonates-related osteonecrosis of the jaw is a side effect that belongs to the broader group of medication-related osteonecrosis of the jaw (MRONJ) and it can occur under the following circumstances: 1) cancer patients undergoing odontological procedures reaching periodontal tissues; 2) poor fitting of dental appliances or poor oral health; 3) parenteral bisphosphonates used for prevention of bone complications due to cancer; 4) bisphosphonates use for longer than 3 to 5 years; 5) concomitant diabetes mellitus or corticosteroids use. It is not possible to grade individual risk for this side effect. There are no reports of such an adverse event during clinical trials [1] [3] [4]. Atypical femur fractures are a complication associated with bilateral chronic bone stress and triggered by minor trauma. They occur under the following circumstances, when associated with bisphosphonates use: a) patients with Asian ethnicity; b) coexistence with lateral bowing of the femur, autoimmune diseases, corticosteroids use; c) bisphosphonates use for longer than 3 years. Their rate declines with the discontinuation of the substances of the class [3]. The risk for jaw osteonecrosis as well as atypical femur fractures is expected to decrease during the "bisphosphonates holiday".

4.3. Usage

"Bisphosphonates holiday" is feasible, based on the premise that these drugs are retained by the skeleton, extending anti-fracture benefits. The "holiday" can be considered either after 5 years or after 10 years of oral therapy (if T score ≤ −2.5 and/or there is a report of a recent fracture) of oral therapy. The effects of a "bisphosphonates holiday" on the risk of bone fracture are unknown [3] [4]. Concomitant supplementation with vitamin D and calcium is recommended, not only for bone health in general but also to reduce the risk of hypocalcemia [5].

5. Ibandronate

5.1. Pharmacology

Ibandronate is a nitrogen-containing bisphosphonate with enough potency and skeletal binding capacity to enable a once-monthly interval dosage [1] [7]. Its pharmacological effect is a cumulative-dependent decrease of bone turnover biochemical markers, as it maintains tissue quality, strength, and architecture, without affecting mineralization and repair properties [1]. An ibandronate struc-

tural formula is depicted in Figure 2.

Clinical effects associated with ibandronate use are: 1) increased lumbar spine and proximal femur BMD and mechanical strength, 2) sustained decrease of bone absorption biochemical markers after three months, and 3) risk reduction of osteoporotic vertebral fractures. Ibandronate consolidated pharmacokinetics parameters are listed below [1] [5]:

- bioavailability: 0.63% (relative to IV administration; reduced by ~90% with food).
- intestinal absorption: impaired by food and beverages (other than plain water).
- Cmax: 49.7 ng/mL (10% of this value is attained after 8 h, due to bone binding, when a slower clearance phase starts as ibandronate returns to the blood to ongoing renal excretion).
- tmax: 0.5 to 2 h.
- bone sequestration rate: 40% to 50% (the remainder being excreted in the urine 24 hours after administration).
- Vd: 90 to 160 L.
- protein binding: 84% to 86% (steady under clinically relevant blood concentration).
- increases in plasma concentration (dose >50 mg): disproportionally greater than dosing.
- half-life: ~1.3 h.
- terminal half-life: 10 to 72 h.
- estimated bone half-life: years.
- renal clearance: 56.9 mL/min (urine excretion linearly related to creatinine clearance).
- fecal excretion: trace amounts.

Ibandronate is not biotransformed [1].

5.2. Indication

In addition to prevention and first-line treatment of postmenopausal osteoporosis, ibandronate is used off-label for the reduction of skeletal events during glucocorticoid chronic use and malignancy hypercalcemia prevention (pathological bone resorption due to bone metastases) [5] [9].

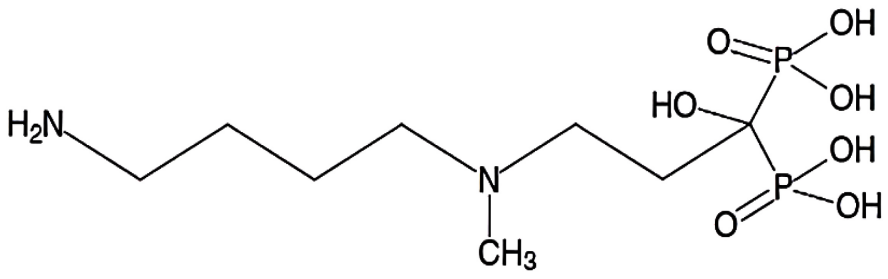

Figure 2. Ibandronate structural formula (adapted from [7]).

5.3. Adherence

Postmenopausal osteoporosis is more common among elderly women and consequently, there is a higher likelihood of concurrent diseases requiring concomitant medication, increasing interactions risk as well as predisposing to adherence and safety concerns. The once-monthly dosage interval, feasible with ibandronate, could minimize these issues among treated patients [7].

5.4. Safety

The most commonly reported adverse reactions with ibandronate are: 1) upper gastrointestinal ulcerations, 2) flu-like symptoms, 3) musculoskeletal symptoms, and 4) nervous system disorders [1] [7]. Immediate adverse events associated with ibandronate share the following characteristics: a) mild to moderate in intensity, b) last 1 to 4 days, and c) did not lead to withdrawal during clinical trials [1]. Once-monthly interval dosage can minimize oesophageal irritation, given the reduced administration frequency [7]. Ibandronate is contraindicated in the following circumstances: i) preexisting gastrointestinal symptoms and disorders (dysphagia, epigastralgia, gastroesophageal reflux disease, gastritis, hiatal hernia), ii) an inability to sit or stand upright for longer than 1 h after administration and iii) creatinine clearance <30 mL/min [1] [3] [4] [5]. No episodes of jaw osteonecrosis were reported with ibandronate [1]. No dose adjustment is necessary during hepatic failure or under a creatinine clearance >30 mL/min [1]. Intestinal absorption is impaired by multivalent cations such as calcium, aluminum, and iron. No pharmacokinetic interactions were demonstrated between ibandronate and other drugs commonly prescribed to postmenopausal women (e.g., tamoxifen and estrogen). Ibandronate interacts with bone-imaging agents used in bone scintigraphy [1] [5].

5.5. Dosage

A recommended regimen is 150 mg once monthly for 3 years [1]. Ibandronate should be taken after 6 hours of fasting (preferentially in the morning) and longer than 1 hour before a meal (with plain water and without any other medications). Patients should not lie down for 60 minutes afterward [1] [3] [5].

6. Cholecalciferol

6.1. Vitamin D Physiology

Cholecalciferol (vitamin D3) is the major form of vitamin D in nature. It is attainable from the following sources: 1) corneocyte membrane 7-dehydrocolesterol, destined for photobiological transformation; 2) regular diet (cod liver oil, mackerel, salmon); 3) as the major form of vitamin D in pharmacological supplements. It can be considered simultaneously as a pre-hormone and a vitamin. Whatever its origin, cholecalciferol is destined to be converted to 25-hydroxyvitamin-D (calcidiol) in the liver by the action of vitamin D-25-hydroxylase. 25-hydroxyvitamin-D is destined to be converted to the biologically active

1,25-dihydroxy vitamin D (calcitriol) by the action of renal vitamin D-1-alpha-hydroxylase. Calcitriol stimulates the synthesis of 25-hydroxyvitamin D-24-hydroxylase, an enzyme that catalyzes the former to inactive calcitroic acid in peripheral cells, the latter destined to be excreted in the bile. Cholecalciferol to calcidiol enzymatic transformation obeys first-order kinetics, *i.e.*, the conversion rate is proportional to the concentration of the former. Nevertheless, 1,25-dihydroxy vitamin D blood levels are strictly controlled through a balance of vitamin D-1-alpha-hydroxylase activity and 25-hydroxyvitamin D-24-hydroxylase catabolic rate in peripheral tissues [10]. On average, the skin releases 250 mcg of cholecalciferol daily, most of it destined either to be excreted in the bile or to be degraded to calcitroic acid, with only 2 mcg converted to bioavailable calcitriol. Physiological actions of calcitriol are: a) to facilitate the active absorption of calcium and phosphate in the small intestine and of calcium in the renal tubules to allow bone mineralization; b) to modulate parathyroid hormone secretion; c) to increase bone reabsorption of calcium and phosphate by increasing RANKL synthesis (a ligand to receptor activator of nuclear factor kappa-B), with subsequent nuclear factor kappa-light chain stimulation and proosteoclast to osteoclast differentiation (under hypocalcemia) [5] [10] [11].

If vitamin D is abruptly interrupted and there is no sun exposure, calcitriol blood levels would still be maintained by two subsequent mechanisms: a) routine calcidiol to calcitriol conversion, the former having a terminal half-life of 2 months; b) cholecalciferol muscle and fat-storage retrieval by the organism [10]. Assuming its biological origin, it is possible to predict the physiological availability of cholecalciferol according to the following factors: 1) skin weight (by inference 7-dehydrocholesterol quantity, inversely proportional to age); 2) skin integrity (the dermal structure is compromised by aging); 3) UVB exposure ("vitamin D winter", earth latitude, weather); 4) fish in the diet; 5) skin melanin quantity (a UVB absorbing molecule); 6) sunscreen use; 7) clothing; 8) glass shielding (a UVB absorbing material). Given the above factors, it is no wonder to verify that vitamin D deficiency is a highly prevalent condition in the western world and, by inference, bone metabolism complications associated with calcitriol decrease, especially among postmenopausal women [11].

6.2. Cholecalciferol Pharmacokinetics

Cholecalciferol absorption takes place in the small intestine, it is fat-dependent and occurs readily. From the former, it is transported inside chylomicrons via the lymphatic system into the bloodstream, and linked to vitamin D binding protein (DBP) thereon. Cholecalciferol consolidated pharmacokinetics parameters are listed below [3] [5] [10]:

- time to conversion to 25-hydroxyvitamin-D3: 10 to 24 hours.
- protein binding rate: 50% to 80%.
- circulating half-life: 2 days.
- functional half-life: 2 to 3 months (influenced by DBP concentration and genetic polymorphisms).

- minimum serum levels for optimal calcium absorption: 30 ng/mL.

Oral cholecalciferol increases intestinal calcium and phosphate absorption in the range of 10% - 15% to 30% - 40% and 60% - 80% rates, respectively [5]. Vitamin D3 pharmacokinetics is unaltered by ibandronate under single dosages of 24,000 IU and 150 mg, respectively [12].

6.3. Safety

Cholecalciferol side effects are generally associated with excessive doses and consist of hypercalcemia, nephrocalcinosis, osteoporosis, non-skeletal calcification, and pancreatitis [5]. According to the American Geriatric Society, 25-hydroxyvitamin D blood levels up to 100 ng/mL can be considered safe. Daily vitamin D dosage can be increased up to 10,000 IU in obese patients, due to fat distribution. Safety of doses ≥400 IU daily during pregnancy is not established. Maternal hypercalcemia may lead to supravalvular aortic stenosis syndrome and suppression of PTH release in the neonate. Excessive amounts of vitamin D in nursing mothers may result in hypercalcemia in infants [5].

6.4. Dosage

The Institutes of Medicine recommends 1500 to 2000 IU of vitamin D daily to treat and prevent postmenopausal osteoporosis [11]. Even though vitamin D and calcium supplementation are universally suggested, there is no consensus on the ideal daily regimens which vary from 600 IU to 1200 IU and 2000 to 2500 mg, respectively, depending on age and institutional recommendations. To attain calcidiol blood levels >30 ng/mL in vitamin D deficient adults in a 5 to 8 weeks term, vitamin D 50,000 IU once a week (or 7000 daily) regimen is suggested [3].

7. Rationale for Ibandronate and Cholecalciferol Combination

The rationale for ibandronate and cholecalciferol fixed-dose combination in the postmenopausal osteoporosis setting is supported by the following aspects.

7.1. Additive Effect

Postmenopausal osteoporosis presents a complex pathophysiology, hinting the indication for different therapeutic modalities. Ibandronate and cholecalciferol fixed-dose combination can be considered clinically feasible for the following reasons: 1) both ibandronate and vitamin D influence at least two important pathophysiological elements related to osteoporosis, *i.e.*, bone unbalanced resorption and low vitamin D availability, respectively; 2) both belong to first-line pharmacological classes recommended for this condition; 3) there is no know interaction between the two.

7.2. Synergistic Effect

Ibandronate decreases the uptake of calcium from bone into the blood, an effect potentially associated with hypocalcemia. By increasing intestinal and renal cal-

cium absorption, cholecalciferol could decrease this risk.

7.3. Therapeutic Adherence

Combining both substances in the same pharmaceutical formulation can simplify the daily medical routine, especially in the setting of a chronic incurable condition, as well as improve adherence.

8. Results

We retrieved a total of 10 general studies and 19 clinical trials on ibandronate and cholecalciferol (16 RCT and 3 non-RCT), the latter ones comprehending a total of 11,218 patients (no epidemiological studies, observational studies, systematic reviews, or meta-analyses were found). Reported research parameters were: 1) comparative tolerability in women previously using weekly bisphosphonates; 2) satisfaction or preference of women in transitioning from weekly bisphosphonate to the studied combination; 3) effect on bone microarchitecture in women with osteopenia; 4) 25-hydroxyvitamin D and bone markers levels; 5) comparative efficacy with weekly alendronate regarding the lumbar spine and total hip BMD; 6) regional distribution of lumbar vertebrae and hip BMD changes; 7) tolerability in general; 8) bone strength, bone metabolism and muscle strength; 9) prevention of bone loss; 10) BMD mantainence after 3 years and 5 years of use. Studies' conclusions reported the combination as a) effective, 8 trials; b) safe and effective, 2 trials; c) safe and non-inferior, 1 trial, d) well tolerated, preferred or satisfying, 4 trials; e) comparable or non-inferior, 2 trials; f) ineffective, 1 trial (2 of 4 endpoints). The studied combination was regarded as safe in 12 trials (non-comparative results, not informed or not applicable, 5 trials). Concentrations of ibandronate and vitamin D varied from 2.5 mg daily/20 mg to 150 mg monthly and 200 IU daily to 24,000 IU monthly, respectively. The findings related to the clinical trials are summarized in **Appendix**.

9. Discussion

Postmenopausal osteoporosis is a chronic and uncurable condition that might compromise all women after their reproductive years. This syndrome's complex pathophysiology makes a multi-target therapeutic approach warranted, with an association of drug combinations and lifestyle changes, as the best possible modality. Ibandronate and cholecalciferol had their individual roles on postomenopausal osteoporosis and osteopenia management already evidenced. Their combination in postmenopausal osteoporosis and osteopenia setting is bound to provide pharmacological additive and synergistic effects as well as comfort to the patient, consistently with the combination management recommended for the condition. One limitation of our study was the uneven regimens of ibandronate and vitamin D used in selected clinical trials. Nevertheless, Cho *et al*. and Yoon *et al*. studies regimens [13] [14] outstood for combining ibandronate and vitamin D, the latter under a 24,000 IU monthly dosage (consistently with therapeu-

tic adherence policies, as well as with the daily dosage range recommended for maintaining sufficient vitamin D levels - 800 to 1000 IU -, as detailed by a recent osteoporosis consensus [3]). Another limitation of our systematic review was the impossibility of providing an overall statistical expression to our findings due to the primary studies' methodological heterogeneity. Notwithstanding, we consider that the grouped analysis of retrieved publications, as well as the combination rationale detailed above, allows us to suggest considering the ibandronate and cholecalciferol combination for postmenopausal osteoporosis and osteopenia management.

10. Conclusion

Based on the results of analyzed clinical trials, we concluded that the combination of ibandronate and cholecalciferol for postmenopausal osteoporosis and osteopenia management is safe and feasible, as well as consistent with the pharmacological combination and adherence approach recommended for the condition.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Acronyms

Cmax: maximal concentration; **CTx:** C-telopeptide of type 1 collagen; **BMD:** bone mineral density; **DBP:** vitamin D binding protein; **DXA:** bone densitometry; **FDS:** farnesyl diphosphate synthase; **FEA:** finite element analysis; **GI:** gastrointestinal; **HSA:** hip structural analysis; **NA:** not applicable; **NI:** not informed; **OPSAT-Q:** Osteoporosis Patient Satisfaction Questionnaire; **QCT:** quantitative computed tomography; **RANKL:** receptor activator of nuclear factor kappa-B ligand; **RCT:** randomized clinical trial; s**CTx:** serum C-telopeptide of type 1 collagen; **tmax:** maximal time; **Vd:** volume of distribution.

Appendix. Selected RCT and Non-RCT with the Combination of Ibandronate and Vitamin D in Osteoporosis and Osteopenia Management

AUTHORS	STUDY OBJECTIVES	REGIMENS	STUDY TYPE	*n*	RESULTS	SAFETY	CONCLUSION
Binkley 2009 (a) [15]	To assess serum CTx levels in postmenopausal women with osteoporosis after 3 days of therapy	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) included vitamin D 400 IU daily and (2) lasted 6 months	Randomized double-blind	$n_A = 49$ $n_B = 17$	Median reductions of serum CTx-1 were: (1) Group A, 70.2% and (2) Group B, 6.0% ($p < 0.0001$) (levels remained consistently below baseline over 6 months)	Ibandronate was well tolerated	Serum CTx-1 was decreased in Group A and remained suppressed below baseline over 6 months
Binkley 2009 (b) [16]	To assess GI tolerability with once-monthly ibandronate in postmenopausal women previously using weekly bisphosphonates	Ibandronate 150 mg once-monthly plus vitamin D (dosage NI), for 6 months	Self-paired	89	Regarding once-monthly ibandronate: (1) >60% of patients reported an improvement in heartburn or acid reflux, (2) >70% reported improvements in stomach upset, and (3) of those patients who complained of stomach upset within 48 h of taking their last weekly bisphosphonate, >80% reported improved overall satisfaction (statistical significance NI for any of the above parameters)	The tested regimen was well tolerated	A majority of women who experienced GI tolerability issues with weekly bisphosphonates reported improvements after transitioning from a weekly bisphosphonate to the tested regimen
Bock 2012 [17]	To assess the impact of monthly ibandronate on bone structure and density in post-menopausal osteoporosis or osteopenia, derived from in vivo microCT	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) included vitamin D 400 IU daily and (2) lasted 12 months	Randomized	$n_A = 36$ $n_B = 34$	Group A: (1) performed better than Group B ($p = 0.045$) (multiple regression analysis of primary endpoints) and (2) reduction in bone turnover ($p < 0.001$) Secondary endpoints (Group A): (1) greater increases in distal tibia cortical thickness, cortical density and total density ($p \leq 0.043$) and (2) greater increases of hip and lumbar DXA-BMD ($p \leq 0.017$)	NI	While there was a greater mineralization in Group A, this effect differed among body regions

Continued

Bonnick 2009 [18]	To assess postmenopausal women's satisfaction with a weekly bisphosphonate transitioned to once-monthly ibandronate in the setting of prevention and treatment of osteoporosis and osteopenia	Ibandronate 150 mg once-monthly plus vitamin D (dosage NI), for 6 months	Self-paired	1678	OPSAT-Q: (1) composite satisfaction score was changed ($p < 0.0001$) and (2) there was improvement in domain scores (convenience, quality of life and overall satisfaction) (all $p < 0.0001$)	Improvement in OPSAT-Q side effects domain score ($p = 0.02$)	Patients previously using weekly bisphosphonates reported improved satisfaction with the tested regimen
Chapurlat 2013 [19]	To assess the effect of once-monthly ibandronate on bone microarchitecture among women with osteopenia	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) included vitamin D 400 IU daily and (2) lasted 24 months	Randomized double-blind	$n_A = 72$ $n_B = 77$	Tibial cortical volumetric BMD in group A was greater at 12 and 24 months (statistical significance NI), with better cortical thickness Areal BMD - group A in comparison to group B: (1) hip and spine was greater at 12 and 24 months ($p < 0.001$) and (2) radius was greater at 24 months ($p = 0.09$)	Most adverse events with group A regimen were the ones expected with bisphosphonates use in general and none were serious	Group A regimen improved tibial cortical volumetric BMD at 12 and 24 months, and preserved tibial cortical thickness
Cho 2015 [11]	To assess the efficacy of once-monthly ibandronate plus cholecalciferol on the levels of 25-hydroxyvitamin D and bone markers among postmenopausal women with osteoporosis	Group A: ibandronate 150 mg once-monthly Group B: ibandronate 150 mg plus cholecalciferol 24,000 IU (both once-monthly) Both regimens for 16 weeks	Randomized double-blind	$n_A = 99$ $n_B = 102$	Group A in comparison to group B ($p < 0.001$) - serum levels: (1) vitamin D increased and (2) CTx decreased	The overall incidence rates of adverse events did not differ significantly between the groups and there were no serious adverse events	Group B regimen may be useful for the amelioration of vitamin D deficiency and decreasing serum levels of resorption markers in patients with postmenopausal osteoporosis

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Emkey 2005 [20]	To assess the preference for once-monthly ibandronate or weekly alendronate among postmenopausal patients with osteoporosis	Sequence A: ibandronate followed by alendronate Sequence B: alendronate followed by ibandronate Both sequences: (1) ibandronate and alendronate under once-monthly 150 mg and weekly 70 mg regimens, respectively, (2) included vitamin D (dosage NI), and (3) had a 3 months duration each	Randomized, open-label and crossed-over	$n_A = 170$ $n_B = 172$	Patients showed superior preference rates for ibandronate ($p < 0.0001$)	Patients who preferred ibandronate chose "it is easier to tolerate side effects" in the questionnaire (statistical significance not calculated)	Significantly more women preferred once-monthly ibandronate than weekly alendronate
Emkey 2009 [21]	To assess the efficacy and tolerability of weekly alendronate versus once-monthly ibandronate among postmenopausal women with osteoporosis (posthoc analysis Miller 2008)	Group A: ibandronate and alendro-nate-matched placebo Group B: alendronate and ibandro-nate-matched placebo Both regimens: (1) 12 months duration, (2) ibandronate and alendronate under once-monthly 150 mg and weekly 70 mg regimens, respectively, and (3) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 887$ $n_B = 873$	Groups A and B, respectively (statistical significance NI): (1) median changes in trough concentrations of sCTx, −75.5% and −81.2% and (2) percentage of responders (mean lumbar spine and hip BMD gains), 90% and 87.5%, and 92% and 90%	GI adverse events were reported in ≤30%	Group A regimen provided clinically comparable efficacy and and GI tolerability compared to group B

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Engelke 2009 [22]	To assess the regional differences of lumbar vertebrae BMD changes among postmenopausal women with osteoporosis	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized	$n_A = 41$ $n_B = 35$	Groups A and B % BMD changes, respectively ($p < 0.05$): (1) total vertebral body, 3.0 and −1.1, (2) vertebral midsection, 2.4 and −1.3, (3) trabecular total vertebral body, 1.2 and −2.8, (4) superior section of the anterior and middle trabecular vertebral body, 1.8 and −3.4 and (5) middle cortical and subcortical vertebral body, 3.5 and −0.3	NI	Group A regimen increased lumbar spine integral and trabecular BMD in comparison to group B
Engelke 2010 [23]	To assess the regional distribution of hip QCT BMD with once-monthly ibandronate among postmenopausal women with osteoporosis (posthoc analysis of Lewiecki 2009)	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 47$ $n_B = 46$	Group A BMD increases in comparison to group B: (1) vertebral superior and inferior trabecular and cortical midsection ($p = 0.032$, 0.055 and 0.014, respectively), (2) total hip (trabecular, cortical and subcortical) ($p = 0.005$, 0.047 and 0.009, respectively), (3) trochanter (trabecular and cortical) ($p = 0.007$ and 0.01, respectively) and (4) trabecular femoral neck ($p = 0.02$)	NA	Group A regimen provided improved vertebral, total hip, trochanter, and femoral neck QCT BMD, in comparison to group B
Lewiecki 2009 [24]	To assess the biomechanical determinants of bone strength among postmenopausal women with osteoporosis under ibandronate	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 47$ $n_B = 46$	Group A had increased, relatively to group B: (1) total hip QCT BMD ($p = 0.005$), (2) DXA areal BMD ($p = 0.003$), (3) FEA-derived hip strength to density ratio ($p < 0.001$), (4) femoral, peripheral, and trabecular strength ($p = 0.001$, 0.011, and 0.003, respectively), (5) vertebral, peripheral, and trabecular strength ($p = 0.001$, 0.001, and 0.023, respectively), (6) anteroposterior bending stiffness ($p = 0.001$) and (7) HSA-estimated femoral narrow neck cross-sectional area and outer diameter ($p = 0.003$, and 0.049, respectively)	NI	Hip and spine BMD and strength, both improved with group A regimen in comparison to group B

Continued

					Group A showed relatively to group B		
McClung 2009 [25]	To assess the prevention of bone loss with ibandronate among postmenopausal women	Group A: ibandronate 150 mg once-monthly Group B: placebo Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 77$ $n_B = 83$	At 3 months - median sCTx reduction, respectively: >55% vs. ~4% (statistical significance NI)	At 12 months: (1) larger increases in lumbar spine BMD ($p < 0.0001$) and (2) lumbar spine BMD change of 0% vs. 38.6%, respectively (statistical significance NI)	Both group's regimens were well tolerated	Group A regimen prevented further bone loss in postmenopausal women with preexisting low bone mass
Miller 2005 [26]	To assess a once-monthly ibandronate regimen in postmenopausal osteoporosis	Group A: 2.5 mg daily Group B: 50 mg in two consecutive days (monthly) Group C: 100 mg monthly Group D: 150 mg monthly All regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 402$ $n_B = 404$ $n_C = 402$ $n_D = 401$	Lumbar BMD: (1) increased in all groups (no statistically significant difference), (2) groups B and C regimens were noninferior to group A regimen and (3) group D regimen was superior to group A regimen ($p = 0.002$) Hip BMD gains were superior in groups C and D regimens in comparison with group A regimen ($p < 0.001$) Serum levels of C-telopeptide: decreased in all groups The proportion of women who achieved predefined threshold levels for BMD % change from baseline (groups C and D): 6% and 3% for lumbar spine and total hip, respectively (statistical significance NI)		All group's regimens were similarly well tolerated	Groups B, C and, D regimens were at least as effective as group A regimen

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Miller 2008 [27]	To assess the non-inferiority of once-monthly ibandronate comparatively to weekly alendronate regarding the lumbar spine and total hip BMD in postmenopausal osteoporosis	Group A: ibandronate 150 mg once-monthly Group B: alendronate 70 mg weekly Both regimens: (1) 12 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	n_A = 887 n_B = 873	BMD increased similarly in both groups (statistical significance for magnitude increase NI), meeting non-inferiority criteria of group A regimen relative to group B regimen	Both regimens were well tolerated	Group A regimen was comparable to group B regimen at increasing lumbar spine and total hip BMD
Miller 2012 [28]	To assess the efficacy of monthly ibandronate in sustaining BMD after 5 years (an extension of Reginster 2006)	Group A: 100 mg monthly Group B: 150 mg monthly Both regimens: (1) 3 years duration (plus the previous 2 years from Reginster 2006), (2) included vitamin D 400 IU daily, and (3) maintained women who showed ≥75% adherence to protocol in Reginster 2006 (Reginster 2006 groups A and B patients were reallocated or randomized to Miller 2012 groups A and B, the former ones being extinguished)	Randomized double-blind	n_A = 358 n_B = 361	Relatively to Reginster 2006 results (statistical differences were not calculated): (1) groups A and B showed 8.2% and 8.4% increase in lumbar spine BMD, respectively, (2) 698 out of 719 patients showed maintenance of proximal femur BMD gains and (3) markers of bone metabolism were stable	There were no tolerability concerns	Groups A and B regimens were both effective and well tolerated for up to 5 years in postmenopausal osteoporosis
Nakamura 2007 [29]	To assess if once-monthly ibandronate is well tolerated and efficacious in Japanese osteoporotic women	Group A: placebo Group B: 20 mg Group C: 50 mg Group D: 100 mg Group E: 150 mg (groups B to E: ibandronate) All regimens: (1) 4 months duration and (2) included vitamin D 200 IU daily	Randomized double-blind	n_A = 28 n_B = 27 n_C = 27 n_D = 26 n_E = 26	Median reductions in urinary CTx from baseline - groups A, B, C, D, and E, respectively: (1) 28.9%, (2) 35.7%, (3) 43.0%, (4) 70.9% and (5) 81.7% Increases in lumbar spine BMD for groups A, B, C, D, and E, respectively: (1) 0.7%, (2) 1.4%, (3) 3.1%, (4) 4.0% and (5) 3.2% (statistical significance NI for none of the above endpoints)	No serious drug-related adverse events were reported	Monthly ibandronate reduces bone turnover and increases lumbar spine BMD in Japanese women with osteoporosis

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Reginster 2006 [30]	To assess the efficacy and tolerability of once-monthly ibandronate in postmenopausal osteoporosis (a continuation of Miller 2005 study)	Group A: 2.5 mg daily Group B: 50 mg in two consecutive days (monthly) Group C: 100 mg monthly Group D: 150 mg monthly All regimens: (1) 24 months duration and (2) included vitamin D 400 IU daily	Randomized double-blind	$n_A = 402$ $n_B = 404$ $n_C = 402$ $n_D = 401$	Lumbar, total hip, and femoral neck BMD increased in all groups (statistically significant difference between groups A and D regimens - $p < 0.001$ and <0.05 - for lumbar and total hip/femoral neck BMD, respectively) sCTx levels: (1) decrease observed after 3 months and sustained up to 24 months in all groups, (2) percentage of patients with a >50% decrease in sCTx from baseline was greater in group D relative to the other groups ($p = 0.002$) and (3) a greater proportion of patients presented sCTx decrease with group D regimen in comparison to group A regimen ($p = 0.006$)	All group's regimens were well tolerated	Groups B, C, and D regimens were at least as effective and well tolerated as group A regimen. Once-monthly administration may improve adherence, thereby optimizing outcomes
Stakkestad 2008 [31]	To assess the efficacy of monthly ibandronate in sustaining BMD improvement after 3 years (an extension of Reginster 2006)	Group A: 100 mg monthly Group B: 150 mg monthly Both regimens: (1) 1-year duration (plus the previous 2 years from Reginster 2006), (2) included vitamin D 400 IU daily, and (3) maintained the women who completed Reginster 2006 (Reginster 2006 groups A and B patients were reallocated or randomized to Stakkestad 2008 groups A and B, the former ones being extinguished)	Randomized double-blind	$n_A = 359$ $n_B = 360$	Relatively to Reginster 2006 for groups A and B, respectively (statistical significance NI): (1) mean lumbar spine BMD increased a further 1.1% and 1.5%, and (2) total hip BMD changed −0.08% and 0.3% Considering a total of 3 years of treatment (Reginster 2006 followed by Stakkestad 2008) for groups A and B, there were: (1) 6.4% and 7.6% increases in lumbar spine BMD, respectively ($p < 0.0001$), (2) 3.4% and 4.1% increases in total hip BMD, respectively ($p < 0.0001$) and (3) sCTx decreased for both groups ($p < 0.001$)	Groups A and B regimens were well tolerated	Group B regimen is an effective and well-tolerated long-term treatment for postmenopausal osteoporosis, with consistent improvement in BMD and bone turnover during 3 years of continuous treatment

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Yoon 2017 [14]	To assess the effects of a combination of ibandronate and cholecalciferol in bone metabolism, muscle strength and BMD in postmenopausal Korean women with osteoporosis	Once-monthly ibandronate 150 mg plus cholecalciferol 24,000 IU for 6 months	Self-paired	62	The following endpoints showed statistically significant changes (serum): (1) 25-hydroxyvitamin D ($p < 0.01$), (2) CTx ($p = 0.03$), and (3) PTH ($p = 0.03$) The following endpoints showed no statistically significant changes: (1) handgrip strength and (2) lumbar and femoral neck BMD	NI	The tested regimen was effective in improving 25-hydroxyvitamin D serum levels and bone metabolism, however, there was no improvement of muscle strength and BMD

CTx: C-telopeptide of type 1 collagen; DXA: bone densitometry; FEA: finite element analysis; GI: gastrointestinal; HSA: hip structural analysis; NA: not applicable; NI: not informed; OPSAT-Q: Osteoporosis Patient Satisfaction Questionnaire; QCT: quantitative computed tomography; RCT: randomized clinical trial; sCTx: serum C-telopeptide of type 1 collagen.