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ABSTRACT

Osteoporosis is the result of bone loss due to an imbalance in bone turnover such that bone resorption exceeds bone formation. Bisphosphonates are potent inhibitors of osteoclast activity that reduce bone turnover and re-establish the balance between bone resorption and formation. In clinical studies, several bisphosphonates prevent bone loss, preserve bone structure, improve bone strength and, in patients with osteoporosis, substantially reduce fracture risk. They are effective in multiple clinical settings including postmenopausal osteoporosis, low bone mass in men and drug-induced bone loss. Intermittent oral dosing and intravenous administration are more convenient than the original daily dosing regimen. These drugs are generally well tolerated and have an excellent safety profile in that serious side effects are uncommon. Potent bisphosphonates are generally the preferred treatment option for most patients with or at risk for osteoporosis. **(Arq Bras Endocrinol Metab 2006;50/4:735-744)**

Keywords: Bisphosphonates; Alendronate; Risedronate; Ibandronate; Osteoporosis

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RESUMO

Bisfosfonatos.

Osteoporose é o resultado da perda óssea devida a um imbalanço no *turnover* ósseo, onde a reabsorção óssea excede sua formação. Os bisfosfonatos são inibidores potentes da atividade osteoclástica, que reduzem o *turnover* ósseo e restabelecem o balanço entre a reabsorção e a formação óssea. Em estudos clínicos, vários bisfosfonatos previnem a perda óssea, preservam sua estrutura, melhoram sua força e substancialmente reduzem o risco de fraturas em pacientes com osteoporose. Eles são efetivos em várias situações clínicas, incluindo a osteoporose pós-menopáusica, a reduzida massa óssea em homens e perda óssea induzida por drogas. Doses orais intermitentes e administração intravenosa são mais convenientes do que o esquema original de doses diárias. Essas drogas são geralmente bem toleradas e têm um excelente perfil de segurança, no qual efeitos colaterais sérios são incomuns. Os bisfosfonatos potentes são geralmente a opção terapêutica preferida para a maioria dos pacientes com ou em risco de osteoporose. **(Arq Bras Endocrinol Metab 2006;50/4:735-744)**

Descritores: Bisfosfonatos; Alendronato; Risedronato; Ibandronato; Osteoporose

OSTEOPOROSIS IS A DISORDER of skeletal fragility due a combination of low bone mass, deteriorated bone architecture and perhaps alterations in other aspects of bone quality (1). Osteoporosis is usually the result of bone loss that occurs after menopause in women and in older men and women. This bone loss is a consequence of increased and unbalanced bone

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remodeling such that bone resorption by osteoclasts exceeds osteoblastic bone formation. Increased bone remodeling reduces bone strength by causing stress risers in thinned trabeculae and increased porosity of cortical bone (2), and high bone turnover is a risk factor for fracture independent of bone density in elderly subjects (3). Thus, there is a strong rational for the use of pharmacologic agents that reduce osteoclastic bone resorption to treat patients with osteoporosis (4).

Bisphosphonates are stable synthetic analogs of pyrophosphate that suppress osteoclast-mediated bone resorption and indirectly decrease osteoblast activity (5). Hence, they should be considered as anti-catabolic drugs in contrast to bone-forming anabolic agents (6). Bisphosphonate therapy normalizes bone turnover, reduces the number of bone remodeling sites and stress risers, restores the balance of bone remodeling, prevents bone loss and deterioration of bone structure and, in patients with osteoporosis, reduces fracture risk (5). This review will focus primarily on the use of the three potent bisphosphonates currently approved by the FDA for the prevention and treatment of osteoporosis.

MECHANISM OF ACTION

Bisphosphonates are administered orally or intravenously. Under ideal conditions, about 1% of the orally administered dose is absorbed. Up to 50% of the absorbed or intravenously-administered dose is quickly taken up by the skeleton (5). The remainder of the drug undergoes renal excretion without metabolism. Bisphosphonates have a long residual half-life (years) in skeletal tissue. The drug retained in the skeleton has relatively little effect since that drug is buried by newly formed bone and isolated from osteoclasts.

Bisphosphonates preferentially bind to the surface of bone at sites of active remodeling and become incorporated into osteoclasts (5). Non-nitrogen-containing bisphosphonates such as clodronate and etidronate inhibit bone resorption by generating a toxic analog of adenosine triphosphate which interferes with mitochondrial function and induces apoptosis of osteoclasts. The potent nitrogen-containing members of this drug class, including alendronate, risedronate, ibandronate, pamidronate and zoledronic acid, inhibit farnesyl diphosphate synthetase, a distal step in the cholesterol synthesis pathway. Its inhibition suppresses the process of protein geranylgeranylation that is essential for the basic cellular processes required for osteoclastic activity. As a result, the recruitment and differentiation of osteoclast precursors is inhibited, attachment of osteoclasts to bone is impaired and the activation of bone remodeling units is reduced. Osteoclast apoptosis is also induced which may contribute to the antiresorptive effect.

Differences in the side-chain structures determine the potency and binding avidity of bisphosphonates to bone mineral in *in vitro* studies (5). Whether these differences translate into different clinical responses is unknown.

SKELETAL EFFECTS OF BISPHOSPHONATES

Oral therapy with bisphosphonates suppresses biochemical indices of bone resorption to about 50% of baseline at one month and to a stable nadir of 50–70% below baseline by three months (7-9). Bone formation falls more slowly, reaching a steady state after six to twelve months of treatment. Overall, bone turnover is reduced to the levels seen in healthy young adults.

Bone mineral density increases modestly (2–6%) during the first year of treatment. Values in the lumbar spine continue to increase at a slower rate for several years, while BMD in the proximal femur plateaus after about two years of treatment (10-12). The initial increase in BMD is a consequence of the reduced number and depth of bone remodeling units (13). Subsequent increase is due to a progressive increase in the mineral density of bone, a consequence of reduced remodeling and increasing age of the bone tissue (14). Therapy preserves but does not increase bone volume or restore bone structure (15,16).

In patients with osteoporosis, bisphosphonate therapy results in clinically relevant reduction in the incidence of vertebral and non-vertebral fractures (including hip fractures) (10,12,17-21). Fracture protection occurs within a few months of beginning therapy (10,12,22-24) and is sustained for at least several years (19,25). Importantly, the cycle of progressive, multiple vertebral fractures is reduced by 77–96% (10,18,20).

The specific mechanisms by which bisphosphonates prevent fracture are not known. The observed effects on fractures exceed the estimates effects based on BMD changes, and the correlation between changes in fracture rates and changes in BMD is, at best, modest (26). Estimates of the contribution of the change in BMD to vertebral fracture reduction with bisphosphonates have ranged from 17–28% (27,28), and no differences in fracture risk reduction are observed with different doses of individual bisphos-

phonates that cause varied BMD responses (12,17,19,21). The time course of fracture reduction more closely follows the effects of treatment on indices of bone turnover than on BMD, and a significant correlation exists between the change in these markers with therapy and fracture protection (29,30). It is likely that the direct effect of bisphosphonates — the suppression of osteoclastic bone resorption — reduces fracture risk by decreasing the number of bone remodeling sites and stress risers, preserving or slightly increasing bone density and maintaining bone structure (5).

SPECIFIC BISPHOSPHONATE DRUGS

The FDA-approved indications and doses of bisphosphonates are summarized in table 1. A summary of the fracture protection effects of the approved bisphosphonate drugs is presented in table 2.

Alendronate

Treatment with 10 mg daily increased BMD by 8.6% in the lumbar spine and 6.5% in the femoral neck after 2 years, and indices of bone turnover were reduced (7). The responses to smaller doses were less marked, and higher doses produced no greater effects (7,31). Reductions in bone turnover and increases in BMD were maintained with treatment for up to 10 years (11,32). Effects on bone density and both the rate and pattern of bone turnover were similar when the full week's dose of alendronate was given on a single day each week compared to standard 10 mg daily dosing (33,34). In women with pre-existing vertebral fractures, alendronate therapy reduced the incidence of vertebral, hip and wrist fractures by about 50% (table 2), and the risk of multiple vertebral fractures was decreased by 90% after 3 years (18). In women without previous vertebral fractures but with low BMD, vertebral fracture risk was reduced by 44% over four years (19). The incidence of clinical osteoporotic fractures (the primary end-point of the study) was reduced from 14.1% with placebo to 12.8% with therapy (p value= 0.13). In the sub-group of those women whose femoral neck bone density T-score value was -2.5 or lower, the incidence of clinical osteoporotic fractures was significantly decreased by 36%. No effect on clinical fracture risk was detected in women with T-score values greater than -2.5. In a separate study, therapy for 1 year significantly reduced the incidence of non-vertebral fractures in women with low bone density (T-score -2 or lower) (35). A reduction in clinically apparent vertebral fractures was seen within the first year of treatment, and protection from hip fracture was evident after 18 months of treatment (22).

In young postmenopausal women without osteoporosis, alendronate 5 mg daily for 6 years prevented bone loss, but no effect on fracture rate was observed in this low risk population (36). Treatment with 10 mg daily prevented bone loss in women who discontinued estrogen therapy (37). In men with low BMD (T-score -2 or lower) treated with 10 mg daily for 2 years, bone density in the spine and hip increased, and vertebral fracture rates decreased (38). The effect was similar in subjects with and without androgen deficiency.

Table 1. FDA-approved indications and doses of bisphosphonates for osteoporosis.

Drug	Trade name	Indication	Approved doses
Alendronate	Fosamax® (Merck, Rahway, NJ)	Treatment of postmenopausal osteoporosis	10 mg daily or 70 mg once weekly
		Prevention of postmenopausal bone loss	5 mg daily or 35 mg once weekly
		Treatment of men with osteoporosis	10 mg daily or 70 mg once weekly
		Treatment of glucocorticoid-induced osteoporosis	5 mg daily; 10 mg daily in postmenopausal women not receiving estrogen
Risedronate	Actonel® (Procter & Gamble, Cincinnati, OH)	Treatment and prevention of postmenopausal osteoporosis	5 mg daily or 35 mg once weekly
		Treatment and prevention of glucocorticoid-induced osteoporosis	5 mg daily
Ibandronate	Boniva® (Hoffman-LaRoche, Nutley, NJ)	Treatment of postmenopausal osteoporosis	2.5 mg daily or 150 mg once monthly po or 3 mg intravenously every 3 months
		Prevention of postmenopausal Osteoporosis	2.5 mg daily or 150 mg once monthly po

Table 2. Effects of FDA-approved bisphosphonates on fracture risk.

Drug	Reference	#Subjects	Average Age (years)	Previous vertebral fractures	Duration of study (years)	Fracture incidence (%)		Relative risk reduction (Confidence intervals)	Comment
						Control group	Treatment group		
VERTEBRAL FRACTURES									
Alendronate	17	994	64	20%	3	6.2%	3.2%	48% (5,72)	A
	18	2027	71	> 96%	2.8	15%	8%	47% (32,59)	B
	19	4432	68	0%	4.2	3%	2%	44% (20,61)	B
Risedronate	10	1628	69	80%	3	16.3%	11.3%	41% (18, 57)	C
	20	814	71	100%	3	29%	18.1%	49% (27, 64)	C
Ibandronate	12	2946	69	94%	3	9.6%	4.7%	52% (28, 68)	D
HIP FRACTURES									
Alendronate	18	2027	71	> 96%	2.8	2.2%	1.1%	51% (1,77)	B
Risedronate	21	5455	74	38%	3	3.2%	1.9%	40% (10,60)	E
Ibandronate	NOT AVAILABLE								

A. pooled alendronate doses; B. 5 mg/day for 2 years, then 10 mg/day; C. 5 mg daily; D. 2.5 mg daily; E. Pooled doses: 2.5 mg and 5 mg daily in women with osteoporosis.

Risedronate

In older postmenopausal women with low bone mass and previous vertebral fracture, treatment with 5 mg daily for 3 years normalized bone turnover. BMD increased by of 5.4% in the lumbar spine and 1.6% in the femoral neck compared to the baseline value (10). The incidence of new vertebral fractures was reduced by 41% to 49% (table 2), and the risk of non-vertebral fractures decreased by 33% to 39% (10,20). Radiographic vertebral fractures were reduced by 61–65% during the first year of therapy, and multiple vertebral deformities were reduced by 77–96% during that interval. The beneficial effect on vertebral fracture risk was evident for at least 5 years (25). Treatment for 3 years decreased the incidence of hip fracture by 40% in women ages 70–79 known to have osteoporosis (21). However, no effect on hip fracture risk was observed in even older women enrolled in the study because of fall-related risk factors. Bone loss was prevented in early postmenopausal women (39). Non-inferiority of a 35 mg weekly dose to standard daily dosing with 5 mg was demonstrated in women with low BMD (8). The BMD response in men was similar to that observed in women (40).

Ibandronate

Oral treatment with 2.5 mg daily reduced indices of bone turnover and increased BMD by 6.5% in the spine (vs. 1.3% with placebo) and 3.4% in the total hip (vs. -0.7% with placebo) after 3 years in postmenopausal women with osteoporosis (11). The incidence of new vertebral fractures was reduced by 51% (table 2). No effect on non-vertebral fracture risk was observed (9.1% with ibandronate and 8.2% in the placebo group). With a dose of 2.5 mg daily, bone density was preserved in young postmenopausal women without osteoporosis. (41) The BMD and bone turnover responses to oral ibandronate 150 mg given once monthly (9) and to an intravenous dose of 3 mg given every 3 months were greater than with daily oral dosing (42). At 12 months, lumbar spine BMD increased 4.8% in patients receiving 3 mg ibandronate every 3 months compared to 3.8% in those receiving 2.5 mg tablets daily.

Comparing the effects of bisphosphonates

Despite marked differences in the *in vitro* potency of drugs, the clinical responses to each of the bisphosphonates discussed above are similar. In the only direct comparison of bisphosphonates, the approved dose of alendronate (70 mg once weekly) produced modestly greater increases in BMD and reduction in indices of bone turnover than did the approved dose of risedronate (35 mg once weekly) in postmenopausal women with low BMD (43). It is unclear whether these differences in clinical "potency" translate into differences in fracture protection. Different doses of the same bisphosphonate result in different BMD and bone turnover responses but similar reductions in fracture risk (12,17,19,21). Because clinical trials with the three bisphosphonates differed significantly in their design and in the populations studied, direct comparisons of the effectiveness of the agents on fracture risk reduction or the rapidity or persistence of responses cannot be made.

Other bisphosphonates

Pamidronate, administered intravenously in doses of 30–60 mg given over 4–24 hours every 3 months transiently suppressed bone turnover and increased bone density in the spine (44). There are no data about fracture protection with this regimen.

Zoledronic acid is being evaluated as a treatment for osteoporosis management as a once-yearly intravenous infusion requiring 15 minutes. BMD increased and bone turnover was suppressed for at least 12 months after a single 4 mg dose in women with osteoporosis. (45). Effects on fracture rates are not yet known.

DOSING

Because bisphosphonates are so poorly absorbed from the gastrointestinal tract and avidly adhere to food beverages and other medications (especially calcium salts or supplements), they should be taken on an empty stomach with 4–8 ounces of plain water at least 30 minutes before taking food, beverages or other medications. To minimize reflux and possible GI symptoms, the patient should not lie down for at least 30 minutes after dosing. Intravenous ibandronate is administered as a 15- to 30-second bolus.

TOLERABILITY AND SIDE EFFECTS

In both clinical trials and in clinical practice, bisphosphonates are very well tolerated when dosed and administered appropriately (46).

Gastrointestinal effects

Gastrointestinal symptoms are the most frequent side effects attributed to bisphosphonate use. Nitrogen-containing bisphosphonates have been associated with esophageal irritation and ulceration, resulting in heartburn, abdominal or chest pain and nausea (47-49). These symptoms usually occur within the first few weeks of therapy. Rare cases of significant gastrointestinal bleeding and esophageal perforation or stricture have been reported. In the clinical trials, upper GI side effects were observed with similar frequency (from 20–40%) in the placebo and active treatment groups (10,12,17). In clinical practice, upper GI symptoms occur in 20–30% of women receiving bisphosphonates. The interpretation of these symptoms is complicated by the high background of upper GI symptoms among older adults. Whether there is a difference in the clinical tolerability of the potent bisphosphonates is unknown. No differences in the frequency of gastrointestinal side effects were observed between daily and weekly or monthly dosing groups in clinical trials (10,33,34).

The mechanism of the esophageal irritation requires both direct exposure of the esophageal mucosa to the drug and an acid environment due to esophageal reflux. Proper dosing minimizes the frequency of symptoms. Therapy with oral nitrogen-containing bisphosphonates is contraindicated in patients with esophageal motility disorders and stricture or who are unable to remain upright after dosing.

Alterations in mineral metabolism

Serum calcium values decreased modestly with bisphosphonate therapy due to the acute suppression of bone resorption (7). The nadir of this effect occurred within the first month of therapy and was associated with an appropriate elevation of serum parathyroid hormone levels. Both calcium and PTH values returned to near baseline levels with continued use. The fall in serum calcium was not associated with symptoms in these calcium- and vitamin D-replete patients. Clinically evident hypocalcemia has been observed with bisphosphonate therapy in patients with vitamin D deficiency or hypoparathyroidism (50,51). Bisphosphonates should not be administered to patients with hypocalcemia or with evidence of vitamin D deficiency.

Skeletal effects

Transient bone pain is infrequently observed soon after beginning alendronate therapy. Because these agents accumulate in the skeleton, concern exists regarding the impairment of bone quality by over-suppressing normal skeletal repair mechanisms or causing excess aging and mineralization of the bone tissue. High doses of alendronate impaired healing of skeletal microdamage in animals, but this was not associated with impaired bone strength (52). The microscopic appearance of bone in bisphosphonate-treated subjects is normal (15,16). Several cases of impaired fracture healing have been reported in humans receiving bisphosphonates for osteoporosis, although most were receiving other agents that altered bone metabolism (53). Treatment for up to 7 years with risedronate and 10 years with alendronate has not been associated with clinical evidence of skeletal harm (11,25,32,54).

Osteonecrosis of the jaw

Non-healing lesions of the jaw, usually following invasive dental procedures or trauma, have been reported in

patients receiving bisphosphonates (55). Almost all (95%) of the patients had cancer-related bone disease, were receiving high dose intravenous zoledronic acid or pamidronate therapy and had or were receiving systemic chemotherapy. Most had evidence of osteomyelitis. A small number of patients with these jaw lesions were receiving therapy for osteoporosis or Paget's disease. The pathogenesis of these lesions is not known. Although it is hypothesized that reduced bone turnover is the cause of this problem, reduced bone turnover has not been demonstrated in these patients, and bone scans suggested increased bone turnover at the affected sites (56,57). If there is an association of jaw osteonecrosis with oral bisphosphonate therapy, the incidence is very low. No cases have been described in the large osteoporosis clinical trials. Routine dental care is recommended for patients receiving bisphosphonates (58). Alendronate therapy appears to limit the complications of osteonecrosis of the proximal femur (59,60), is beneficial in patients with periodontal disease (61,62) and did not compromise success of dental implants in a small group of patients (63).

Acute phase reaction

Intravenous or high-dose oral therapy with nitrogen-containing bisphosphonates may be associated with an acute phase reaction manifested by fever, myalgias and lymphopenia lasting a few days (9,42,45,60). This generally occurs with the initial but not subsequent doses.

Other effects

Inflammation of ocular structures, allergic manifestations and abnormal tests of liver function have been reported in patients receiving bisphosphonates (46). These effects were generally mild and abated when therapy was discontinued. Renal failure can occur following rapid intravenous administration of bisphosphonates (65,66).

BISPHOSPHONATE THERAPY IN OTHER FORMS OF OSTEOPOROSIS

Drug-induced bone loss

Bone loss and increased fracture risk accompanies chronic glucocorticoid therapy. In men and women receiving glucocorticoids, treatment with alendronate 5 or 10 mg daily preserved bone density and, after 2 years, reduced the incidence of new vertebral fractures (67). Treatment of patients just beginning or remaining on long-term glucocorticoid therapy with risedronate 5 mg daily preserved or increased bone density and decreased vertebral fracture incidence by 70% during the first year of therapy (68).

Rapid bone loss and vertebral fractures are common complications of glucocorticoid and immunosuppressive therapy following organ transplantation. Bisphosphonate treatment blunts that bone loss, reduces fracture risk and is used routinely in many transplant centers (69,70).

Bone loss and fractures are consequences of chemotherapy or endocrine ablative therapy with aromatase inhibitors in women with breast cancer and GnRH therapy for men with prostate cancer. Bisphosphonate therapy prevents or blunts bone loss in these patients (71-75).

Children with osteoporosis

Small series of children with juvenile osteoporosis treated with bisphosphonates have been reported with apparent clinical benefit (76). In children with osteogenesis imperfecta treated with intermittent intravenous pamidronate or oral alendronate, significant increases in bone density and reduction of fracture incidence were reported without impairment of skeletal growth (77,78). The effects of bisphosphonate treatment in children receiving glucocorticoid therapy have not been evaluated (79).

Premenopausal women

There are few indications for bisphosphonate use in premenopausal women except for those receiving high-dose glucocorticoid therapy. In patients with eating disorders or estrogen-replete premenopausal women with idiopathic osteoporosis, bone resorption rates are slightly increased but formation rates are depressed (80,81). Treating these patients with bisphosphonates reduces bone resorption and slightly increases BMD, but it is unclear that this reduces fracture risk (82,83). Because concern exists about the use of bisphosphonate in women of child-bearing potential, the use of these agents in women of child-bearing age seems appropriate only when a strong clinical justification exists (84).

HOW LONG BISPHOSPHONATE TREATMENT BE CONTINUED?

The appropriate duration of therapy is dictated by the effectiveness of continued treatment compared to what occurs when the drug is stopped. No waning of effect has been demonstrated with continuous bisphosphonate use for at least 10 years (11,25,32,54). Within the first year of stopping alendronate or risedronate after 2 years of treatment in early postmenopausal women, indices of bone turnover returned toward baseline, and bone loss resumed at a rate similar to the control group (39,85). In contrast, discontinuing alendronate therapy in older women who were treated with alendronate for

two to five years resulted in stable BMD and persistent suppression of bone turnover for up to 5 years (11,32,86). This raises the possibility of limiting alendronate therapy to five years. Data on the effect of continuation versus discontinuation on fracture risk are needed before making definitive recommendations regarding the optimal length of alendronate treatment. In the extension of the Phase III alendronate study, fracture rates in patients who discontinued therapy after 5 years were not able to be assessed adequately because of the absence of a placebo group after 3 years (11). In the 3-year analysis of the extension of the Fracture Intervention Trial in which patients who received alendronate therapy for 3–6 years were randomly assigned to either continue or stop therapy, fracture rates were not assessed (32). Fracture data from the 5-year follow-up are awaited. Until that time, continuing alendronate therapy seems justified for patients at high risk for fracture. No published data exist regarding the effects of discontinuing other bisphosphonates in patients with osteoporosis. Due to the variability in the binding avidity to mineral crystal that exists among the bisphosphonate compounds, it is theoretically possible that there may be differences among these drugs in the duration of effect upon discontinuation.

COMBINING BISPHOSPHONATES WITH OTHER ANTIRESORPTIVE AGENTS

Small additional increments in BMD occurred when bisphosphonates were combined with estrogen or raloxifene (87-89), but the effects of these agents are not additive or synergistic. Whether combination therapy provides additional fracture protection is unproven. The routine use of antiresorptive agents in combination is not recommended (90).

CONCLUSIONS

Bisphosphonate therapy corrects the imbalance in bone remodeling that causes loss of bone tissue, prevents bone loss and preserves the integrity of bone structure. The response is rapid and sustained. Protection from both spine and hip fractures in patients with osteoporosis is well documented, and the drugs are very well tolerated. Convenient dosing regimens now exist. On the basis of these attributes, bisphosphonates have become important treatment option for the prevention and treatment of various forms of osteoporosis.

REFERENCES

1. NIH Consensus Development Panel. Osteoporosis prevention, diagnosis and treatment. **JAMA 2001**;285:785-95.
2. Seeman E, Delmas PD. Bone quality — the material and structural basis of bone strength and fragility. **N Engl J Med 2006**;354:2250-61.
3. Garnero P, Hausherr E, Chapuy MC, Marcelli C, Grandjean H, Muller C, et al. Markers of bone resorption predict hip fractures in elderly women: The EPIDOS prospective study. **J Bone Miner Res 1996**;11:1531-8.
4. Kanis JA, Gertz BJ, Singer F, Ortolani S. Rationale for the use of alendronate in osteoporosis. **Osteoporos Int 1995**;5:1-13.
5. Reszka AA, Rodan GA. Mechanism of action of bisphosphonates. **Curr Osteoporos Rep 2003**;1:45-52.
6. Riggs BL, Parfitt AM. Drugs used to treat osteoporosis: the critical need for a uniform nomenclature based on their action on bone remodeling. **J Bone Miner Res 2005**;20:177-84.
7. Chesnut CH 3rd, McClung MR, Ensrud KE, Bell NH, Genant HK, Harris ST, et al. Alendronate treatment of the postmenopausal osteoporotic woman: Effect of multiple dosages on bone mass and bone remodeling. **Am J Med 1995**;99:144-52.
8. Harris ST, Watts NB, Li Z, Chines AA, Hanley DA, Brown JP. Two-year efficacy and tolerability of risedronate once a week for the treatment of women with postmenopausal osteoporosis. **Curr Med Res Opin 2004**;20:757-64.
9. Miller PD, McClung MR, Macovei L, Stakkestad JA, Luckey M,Bonvoisin B, et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: one year results from the MOBILE study. **J Bone Miner Res 2005**;20:1315-22.
10. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M, et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis. **JAMA 1999**;282:1344-52.
11. Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, et al. Ten years' experience with alendronate for osteoporosis in postmenopausal women. **N Engl J Med 2004**;350:1189-99.
12. Chesnut III CH, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A, et al. Ibandronate: a comparison of oral daily dosing versus intermittent dosing in postmenopausal osteoporosis. **J Bone Miner Res 2004**; 19:1241-9.
13. Heaney RP. The bone-remodeling transient: Implications for the interpretation of clinical studies of bone mass changes. **J Bone Miner Res 1994**;9:1515-23.
14. Boivin GY, Chavassieux PM, Santora AC, Yates J, Meunier PJ. Alendronate increases bone strength by increasing the mean degree of mineralization of bone tissue in osteoporotic women. **Bone 2000**;27:687-94.
15. Borah B, Dufresne TE, Ritman EL, Jorgensen SM, Liu S, Chmielewski PA, et al. Long-term risedronate treatment normalizes mineralization and continues to preserve trabecular architecture: Sequential triple biopsy studies with micro-computed tomography. **Bone 2006**;39:345-52.

16. Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ. Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. **J Clin Invest 1997**;100:1475-80.

17. Liberman UA, Weiss SR, Broll J, Minne HW, Quan H, Bell NH, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. **N Engl J Med 1995**;333:1437-43.

18. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. **Lancet 1996**;348:1535-41.

19. Cummings SR, Black DM, Thompson DE, Applegate WB, Barrett-Connor E, Musliner TA, et al. Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures. Results from the Fracture Intervention Trial. **JAMA 1998**;280:2077-82.

20. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML, et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. **Osteoporos Int 2000**;11:83-91.

21. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C, et al. Effect of risedronate on the risk of hip fracture in elderly women. **N Engl J Med 2001**; 344:333-40.

22. Black DM, Thompson DE, Bauer DC, Ensrud K, Musliner T, Hochberg MC, et al. Fracture risk reduction with alendronate in women with osteoporosis: The Fracture Intervention Trial. **J Clin Endocrinol Metab 2000**;85:4118-24.

23. Roux C, Seeman E, Eastell R, Adachi J, Jackson RD, Felsenberg D, et al. Efficacy of risedronate on clinical vertebral fractures within six months. **Curr Med Res Opin 2004**;20:433-9.

24. Harrington JT, Ste-Marie LG, Brandi ML, Civitelli R, Fardellone P,Grauer A, et al. Risedronate rapidly reduces the risk for nonvertebral fractures in women with postmenopausal osteoporosis. **Calcif Tissue Int 2004**;74:129-35.

25. Mellstrom DD, Sorensen OH, Goemaere S, Roux C, Johnson TD, Chines AA. Seven years of treatment with risedronate in women with postmenopausal osteoporosis. **Calcif Tissue Int 2004**;75:462-8.

26. Wasnich RD, Miller PD. Antifracture efficacy of antiresorptive agents are related to changes in bone density. **J Clin Endocrinol Metab 2000**;85:231-6.

27. Cummings SR, Karpf DB, Harris F, Genant HK, Ensrud K, LaCroix AZ, et al. Improvement in spine bone density and reduction in risk of vertebral fractures during treatment with antiresorptive drugs. **Am J Med 2002**;112:281-9.

28. Watts NB, Cooper C, Lindsay R, Eastell R, Manhart MD, Barton IP, et al. Relationship between changes in bone mineral density and vertebral fracture risk associated with risedronate: greater increases in bone mineral density do not relate to greater decreases in fracture risk. **J Clin Densitom 2004**;7:255-61.

29. Eastell R, Barton I, Hannon RA, Chines A, Garnero P, Delmas PD. Relationship of early changes in bone resorption to the reduction in fracture risk with risedronate. **J Bone Miner Res 2003**;18(6):1051-6.

30. Bauer DC, Garnero P, Hochberg MC, Santora A, Delmas P, Ewing SK, et al. Pretreatment levels of bone turnover and the antifracture efficacy of alendronate: the fracture intervention trial. **J Bone Miner Res 2006**; 21:292-9.

31. McClung M, Clemmesen B, Daifotis A, Gilchrist NL, Eisman J,Weinstein RS, et al. The use of alendronate for prevention of postmenopausal osteoporosis. **Ann Intern Med 1998**;128:253-61.

32. Ensrud KE, Barrett-Connor EL, Schwartz A, Santora AC, Bauer DC, Suryawanshi S, et al. Randomized trial of effect of alendronate continuation versus discontinuation in women with low BMD: results from the Fracture Intervention Trial long-term extension. **J Bone Miner Res 2004**;19:1259-69.

33. Schnitzer T, Bone HG, Crepaldi G, Adami S, McClung M, Kiel D, et al. Therapeutic equivalence of alendronate 70 mg once-weekly and alendronate 10 mg daily in the treatment of osteoporosis. **Aging Clin Exp Res 2000**;12:1-12.

34. Luckey MM, Gilchrist N, Bone HG, Davie MW, de Villiers TJ, Wu M, et al. Therapeutic equivalence of alendronate 35 milligrams once weekly and 5 milligrams daily in the prevention of postmenopausal osteoporosis. **Obstet Gynecol 2003**;101:711-21.

35. Pols HA, Felsenberg D, Hanley DA, Stepan J, Munoz-Torres M, Wilkin TJ, et al. Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. **Osteoporos Int 1999**;9:461-8.

36. McClung MR, Wasnich RD, Hosking DJ, Christiansen C, Ravn P, Wu M, et al. Prevention of postmenopausal bone loss: six-year results from the early postmenopausal intervention cohort. **J Clin Endocrinol Metab 2004**;89:4879-85.

37. Ascott-Evans BH, Guanabens N, Kivinen S, Stuckey BG, Magaril CH, Vandormael K, et al. Alendronate prevents loss of bone density associated with discontinuation of hormone replacement therapy: a randomized controlled trial. **Arch Intern Med 2003**;163:789-94.

38. Orwoll E, Ettinger M, Weiss S, Miller P, Kendler D, Graham J, et al. Alendronate for the treatment of osteoporosis in men. **N Engl J Med 2000**;343:604-10.

39. Mortensen L. Charles P, Bekker PJ, Digennaro J, Johnston CC Jr. Risedronate increases bone mass in an early postmenopausal population: two years of treatment plus one year of follow-up. **J Clin Endocrinol Metab 1998**;83:396-402.

40. Ringe JD, Faber H, Farahmand P, Dorst A. Efficacy of risedronate in men with primary and secondary osteoporosis: results of a 1-year study. **Rheumatol Int 2006**;26:427-31.

41. McClung MR, Wasnich RD, Recker R, Cauley JA, Chesnut CH 3rd, Ensrud KE, et al. Oral daily ibandronate prevents bone loss in early postmenopausal women without osteoporosis. **J Bone Miner Res 2004**;19:11-8.

42. Delmas PD, Adami S, Strugala C, Stakkestad JA, Reginster JY, Felsenberg D, et al. Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. **Arthritis Rheum 2006**;54:1838-46.

43. Rosen CJ, Hochberg MC, Bonnick SL, McClung M, Miller P, Broy S, et al. Treatment with once-weekly alendronate 70 mg compared with once-weekly risedronate 35 mg in women with postmenopausal osteoporosis: a randomized double-blind study. **J Bone Miner Res 2005**;20:141-51.

44. Younes H, Farhat G, el-Hajj Fuleihan G. Efficacy and tolerability of cyclical intravenous pamidronate in patients with low bone mass. **J Clin Densitom 2002**;5:143-9.

45. Reid IR, Brown JP, Burckhardt P, Horowitz Z, Richardson P, Trechsel U, et al. Intravenous zoledronic acid in postmenopausal women with low bone mineral density. **N Engl J Med 2002**;346:653-61.

46. Liberman UA. Long-term safety of bisphosphonate therapy for osteoporosis: a review of the evidence. **Drugs Aging 2006**;23:289-98.

47. Bauer DC, Black D, Ensrud K, Thompson D, Hochberg M, Nevitt M, et al. Upper gastrointestinal tract safety profile of alendronate: the Fracture Intervention Trial. **Arch Intern Med 2000**;160:517-25.

48. Hamilton B, McCoy K, Taggart H. Tolerability and compliance with risedronate in clinical practice. **Osteoporos Int 2003**;14:259-62.

49. Epstein S, Delmas PD, Emkey R, Wilson KM, Hiltbrunner V, Schimmer RC. Oral ibandronate in the management of postmenopausal osteoporosis: review of upper gastrointestinal safety. **Maturitas 2006**;54:1-10.

50. Kashyap AS, Kashyap S. Hypoparathyroidism unmasked by alendronate. **Postgrad Med J 2000**;76:417-8.

51. Maalouf NM, Heller HJ, Odvina CV, Kim PJ, Sakhaee K. Bisphosphonate-induced hypocalcemia: report of 3 cases and review of literature. **Endocr Pract 2006**;12:48-53.

52. Li J, Mashiba T, Burr DB. Bisphosphonate treatment suppresses not only stochastic remodeling but also the targeted repair of microdamage. **Calcif Tissue Int 2001**;69:281-6.

53. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. **J Clin Endocrinol Metab 2005**;90:1294-301.

54. Sambrook PN, Rodriguez JP, Wasnich RD, Luckey MM, Kaur A, Meng L, et al. Alendronate in the prevention of osteoporosis: 7-year follow-up. **Osteoporos Int. 2004**;15:483-8.

55. Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. **Ann Intern Med 2006**;144:753-61.

56. Hansen T, Kunkel M, Weber A, Kirkpatrick JC. Osteonecrosis of the jaws in patients treated with bisphosphonates — histomorphologic analysis in comparison with infected osteoradionecrosis. **J Oral Pathol Med 2006**;35:155-60.

57. Chiandussi S, Biasotto M, Dore F, Cavalli F, Cova M, Di Lenarda R. Clinical and diagnostic imaging of bisphosphonate-associated osteonecrosis of the jaws. **Dentomaxillofac Radiol 2006**;35:236-43.

58. Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo SB. Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper. **J Am Dent Assoc 2005**;136:1658-68.

59. Agarwala S, Jain D, Joshi VR, Sule A. Efficacy of alendronate, a bisphosphonate, in the treatment of AVN of the hip. A prospective open-label study. **Rheumatology (Oxford) 2005**;44:352-9.

60. Lai KA, Shen WJ, Yang CY, Shao CJ, Hsu JT, Lin RM. The use of alendronate to prevent early collapse of the femoral head in patients with nontraumatic osteonecrosis. A randomized clinical study. **J Bone Joint Surg Am 2005**;87:2155-9.

61. Lane N, Armitage GC, Loomer P, Hsieh S, Majumdar S, Wang HY, et al. Bisphosphonate therapy improves the outcome of conventional periodontal treatment: results of a 12-month, randomized, placebo-controlled study. **J Periodontol 2005**;76:1113-22.

62. Rocha ML, Malacara JM, Sanchez-Marin FJ, Vazquez de la Torre CJ, Fajardo ME. Effect of alendronate on periodontal disease in postmenopausal women: a randomized placebo-controlled trial. **J Periodontol 2004**;75:1579-85.

63. Jeffcoat MK. Safety of oral bisphosphonates: controlled studies on alveolar bone. **Int J Oral Maxillofac Implants 2006**;21:349-53.

64. Adami S, Bhalla AK, Dorizzi R, Montesanti F, Rosini S, Salvagno G, et al. The acute phase response after bisphosphonate administration. **Calcif Tissue Int 1987**;41:326-31.

65. Banerjee D, Asif A, Striker L, Preston RA, Bourgoignie JJ, Roth D. Short-term, high-dose pamidronate-induced acute tubular necrosis: the postulated mechanisms of bisphosphonate nephrotoxicity. **Am J Kidney Dis 2003**;41:E18.

66. Markowitz GS, Fine PL, Stack JI, Kunis CL, Radhakrishnan J, Palecki W, et al. Toxic acute tubular necrosis following treatment with zoledronate (Zometa). **Kidney Int. 2003**;64:281-9.

67. Adachi JD, Saag KG, Delmas PD, Liberman UA, Emkey RD, Seeman E, et al. Two-year effects of alendronate on bone mineral density and vertebral fracture in patients receiving glucocorticoids: a randomized, double-blind, placebo-controlled extension trial. **Arthritis Rheum 2001**;44:202-11.

68. Wallach S, Cohen S, Reid DM, Hughes RA, Hosking DJ, Laan RF, et al. Effects of risedronate treatment on bone density and vertebral fracture in patients on corticosteroid therapy. **Calcif Tissue Int 2000**;67:277-85.

69. Cohen A, Shane E. Osteoporosis after solid organ and bone marrow transplantation. **Osteoporos Int 2003**;14:617-30.

70. Coco M, Glicklich D, Faugere MC, Burris L, Bognar I, Durkin P, et al. Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate. **J Am Soc Nephrol 2003**;14:2669-76.

71. Fuleihan Gel-H, Salamoun M, Mourad YA, Chehal A, Salem Z, Mahfoud Z, et al. Pamidronate in the prevention of chemotherapy-induced bone loss in premenopausal women with breast cancer: a randomized controlled trial. **J Clin Endocrinol Metab 2005**;90:3209-14.

72. Theriault RL. Strategies to prevent chemotherapy-induced bone loss in women with breast cancer. **Clin Breast Cancer 2005**;5(2):S63-70.

73. Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. **N Engl J Med 2001**;345:948-55.

74. Smith MR, Eastham J, Gleason DM, Shasha D, Tchekmedyian S, Zinner N. Randomized controlled trial of zoledronic acid to prevent bone loss in men receiving androgen deprivation therapy for nonmetastatic prostate cancer. **J Urol 2003**;169:2008-12.

75. Yaturu S, DjeDjos S, Alferos G, Deprisco C. Bone mineral density changes on androgen deprivation therapy for prostate cancer and response to antiresorptive therapy. **Prostate Cancer Prostatic Dis 2006**;9:35-8.

76. Gandrud LM, Cheung JC, Daniels MW, Bachrach LK. Low-dose intravenous pamidronate reduces fractures in childhood osteoporosis. **J Pediatr Endocrinol Metab 2003**;1687-92.

77. Rauch F, Travers R, Glorieux FH. Pamidronate in children with osteogenesis imperfecta: histomorphometric effects of long-term therapy. **J Clin Endocrinol Metab 2006**;91:511-6.

78. Vyskocil V, Pikner R, Kutilek S. Effect of alendronate therapy in children with osteogenesis imperfecta. **Joint Bone Spine 2005**;72:416-23.

79. Brown JJ, Zacharin MR. Proposals for prevention and management of steroid-induced osteoporosis in children and adolescents. **J Paediatr Child Health 2005**;41:553-7.

80. Bolton JG, Patel S, Lacey JH, White S. A prospective study of changes in bone turnover and bone density associated with regaining weight in women with anorexia nervosa. **Osteoporos Int. 2005**;16:1955-62.

81. Donovan MA, Dempster D, Zhou H, McMahon DJ, Fleischer J, Shane E. Low bone formation in premenopausal women with idiopathic osteoporosis. **J Clin Endocrinol Metab 2005**;90:3331-6.

82. Miller KK, Grieco KA, Mulder J, Grinspoon S, Mickley D, Yehezkel R, et al. Effects of risedronate on bone density in anorexia nervosa. **J Clin Endocrinol Metab 2004**;89:3903-6.

83. Golden NH, Iglesias EA, Jacobson MS, Carey D, Meyer W, Schebendach J, et al. Alendronate for the treatment of osteopenia in anorexia nervosa: a randomized, double-blind, placebo-controlled trial. **J Clin Endocrinol Metab 2005**;90:3179-85.

84. Khan A. Management of low bone mineral density in premenopausal women. **J Obstet Gynaecol Can 2005**;27:345-9.

85. Wasnich RD, Bagger YZ, Hosking DJ, McClung MR, Wu M, Mantz AM, et al. Changes in bone density and turnover after alendronate or estrogen withdrawal. **Menopause 2004**;1:622-30.

86. Greenspan SL, Emkey RD, Bone HG, Weiss SR, Bell NH, Downs RW, et al. Significant differential effects of alendronate, estrogen, or combination therapy on the rate of bone loss after discontinuation of treatment of postmenopausal osteoporosis. A randomized, double-blind, placebo-controlled trial. **Ann Intern Med. 2002**;137:875-83.

87. Bone HG, Greenspan SL, McKeever C, Bell N, Davidson M, Downs RW, et al. Alendronate and estrogen effects in postmenopausal women with low bone mineral density. **J Clin Endocrinol Metab 2000**;85:720-6.

88. Harris ST, Eriksen EF, Davidson M, Ettinger MP, Moffett Jr AH Jr, Baylink DJ, et al. Effect of combined risedronate and hormone replacement therapies on bone mineral density in postmenopausal women. **J Clin Endocrinol Metab 2001**;86:1890-7.

89. Greenspan SL, Resnick NM, Parker RA. Combination therapy with hormone replacement and alendronate for prevention of bone loss in elderly women: a randomized controlled trial. **JAMA 2003**;289:2525-33.

90. Binkley N, Krueger D. Combination therapy for osteoporosis: considerations and controversy. **Curr Osteoporos Rep 2005**;3:150-4.

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