Prevalent and Emerging Therapies for Osteoporosis

Lt Col KS Brar*

Abstract

Osteoporosis and fractures associated with it constitute a real and serious socio-medical problem, which only recently has come to the forefront of social consciousness. With increasing number of exservicemen and their dependents, osteoporosis management has become very important in our setup. Currently available pharmacological therapies for prevention of fragility fractures are limited in scope, efficacy and acceptability to patients. Oral bisphosphonates are the standard treatment for osteoporosis which are associated with significant gastrointestinal side effects and thus poor patient compliance. Newer regimens, including intravenous (IV) formulations of bisphosphonates, have successfully come in vogue with greater patient compliance and equal or better benefits. The real need in osteoporosis treatment is for additional anabolic drugs. The only currently approved anabolic agent for treating osteoporosis is teriparatide (recombinant human parathyroid hormone 1-34), which stimulates new bone formation. Considerable efforts are being made to develop new, more effective treatment for osteoporosis. These novel drugs under trial include those primarily inhibiting osteoclastic bone resorption (like bisphosphonates) such as inhibitors of receptor activator of nuclear factor-kappa B ligand (RANKL) signalling, cathepsin K inhibitors, c-Src kinase inhibitors, integrin inhibitors, chloride channel inhibitors and the drugs with osteo-anabolic actions such as orally active parathyroid hormone (PTH) analogues, calcium sensing receptor antagonists, PTH-related peptide analogues and agents that induce osteoblast anabolism via pathways involving key, recently identified, molecular targets (wnt low-density lipoprotein receptor-related protein-5 signalling; sclerostin antibodies).

MJAFI 2010; 66 : 249-254

Key Words : Osteoporosis; Prevalent; Emerging therapies

Introduction

Osteoporosis is by far the most common metabolic bone disease. It is defined as “a disease characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk.” Although it is important to relieve pain and to limit the impact of deformities in established osteoporosis, the primary goal of treatment is to prevent fractures. Prevention and treatment of osteoporosis consists of non-pharmacological and pharmacological therapy. The benefits of three components to the non-pharmacological therapy of prevention of osteoporosis are well established, which include diet, regular weight-bearing exercises and cessation of smoking and alcohol consumption. Diet should include sufficient but not excess of proteins, rich in vitamin C and K and required amount of calcium and vitamin D. In addition, affected patients should avoid, if possible, drugs that increase bone loss, such as glucocorticoids.

Pharmacological Therapy

Most of the therapies for osteoporosis, which are presently approved by United States food and drug

administration (US-FDA), have focused almost exclusively on inhibition of osteoclastic recruitment and activation. These therapies have been found to be effective in reducing bone loss and preventing fractures in osteoporotic patients. The only therapy presently available that stimulates osteoblastic activity is teriparatide (recombinant human parathyroid hormone 1-34). It effectively increases bone mineral density and prevents fragility fracture when given for up to maximum two years. Various therapeutic modalities available are given below.

Calcium and Vitamin D supplementation

The calcium intake recommended for prevention and treatment of osteoporosis range is 1-2 g/day. Most studies indicate that calcium supplementation slows bone loss, but there is limited evidence that calcium supplementation alone can decrease fracture risk. In fact a recent trial has shown increased risk of fractures in osteoporotic patients who were treated with calcium monotherapy [1].

Vitamin D intake should be at least 400 U/day. Vitamin D along with calcium supplementation increases bone mass, decreases seasonal bone loss and can decrease

*Classified Specialist (Medicine & Endocrinology), Command Hospital (EC), Kolkata-27.

the incidence of fractures, particularly in population likely to have deficient intake or limited sun exposure. In these patients supplementation with vitamin D can be achieved equally well with daily, weekly or monthly dosing [2].

Bisphosphonates

Bisphosphonates are pyrophosphate analogues that bind to bone mineral and are then taken up by osteoclasts and rapidly inhibit bone resorption. Alendronate and risedronate are approved for prevention and treatment of osteoporosis on the basis of evidence that they decrease bone resorption, increase bone mass in the spine and hip and decrease the incidence of fractures. Bisphosphonates can prevent bone loss in patients receiving glucocorticoids and in osteoporotic men. There is no consensus on the duration of therapy, but continued benefit has been observed in patients treated for up to 10 years [3]. Bisphosphonates are poorly absorbed orally and must be taken on an empty stomach with no food or other medication. Their gastrointestinal side effects may be reduced by giving bisphosphonates weekly instead of daily. This problem may be circumvented by using parenteral bisphosphonates.

Hormone Replacement Therapy

The role of hormone replacement therapy (HRT) for the prevention and treatment of osteoporosis has been altered substantially by the findings of the large Women's Health Initiative (WHI) clinical trial as well as a number of other controlled trials. The finding that the risk of cardiovascular disease as well as breast cancer was increased, although fracture risk was decreased, has shifted the risk/benefit ratio and substantially decreased the use of HRT [4]. Thus, while HRT is still considered appropriate for the treatment of menopausal symptoms, prevention of osteoporosis is no longer considered an appropriate indication. Also, in contrast to bisphosphonate therapy, there is often accelerated bone loss after withdrawal of estrogen therapy [5].

Calcitonin

Calcitonin, an inhibitor of bone resorption, can increase bone mass, particularly in association with high turnover rates. Calcitonin also has some analgesic properties and may be particularly useful in patients with recent painful vertebral fractures. It is available either for subcutaneous injection or as a nasal spray. The former preparation is probably more effective but is less well tolerated, often producing gastrointestinal side effects. In a three-year randomized trial, nasal calcitonin at 200 U/day was found to decrease fracture incidence significantly, although the effects on bone turnover and bone mass were diminished by the end of the study [6]. Also nasal calcitonin is less effective in increasing BMD

than alendronate. Oral preparation of calcitonin has also been recently approved for treatment of osteoporosis. Calcitonin has been used acutely to reduce pain in patients with vertebral fractures.

Selective Estrogen Receptor Modulators

A number of compounds have had effects similar to those of estrogen on bone, but they act as antagonists in the breast and hence have been called selective estrogen receptor modulators (SERMs). Tamoxifen has been shown to diminish bone loss in women with breast cancer. Another SERM, raloxifene, has not only prevented bone loss but has also reduced the risk of vertebral fracture in osteoporotic patients. Its effects on bone turnover and bone mass are somewhat less than those of estrogen. Raloxifene does not stimulate the breast or uterus and appears to decrease the risk of breast cancer. It reduces low-density lipoprotein (LDL) levels but does not increase high-density lipoprotein (HDL). However, it is associated with an increased risk of thromboembolism and may produce hot flashes. New SERMs, like bazedoxifene acetate, with potentially greater effects in bone are currently being studied.

Anabolic Therapy

Parathyroid hormone

The use of intermittent low-dose synthetic PTH (teriparatide) in both men and women with osteoporosis has produced a substantial increase in trabecular bone mass with little loss or even a gain in cortical bone in the femur and has reduced the incidence of fractures. Treatment with PTH is likely to be the most effective approach in patients who lose bone or continue to have fractures on anti-resorptive therapy. PTH may be particularly useful in glucocorticoid-induced osteoporosis. PTH must be given 20 µg daily as subcutaneous injection and patients must be monitored carefully for hypercalcemia and hypercalciuria. PTH therapy is recommended to be given for 12-18 months. Teriparatide is marketed in India as Inj Forteo (each pre filled syringe costing Rs.22000/- lasts for 28 days) and in vial form as Inj Bonista (each vial costing Rs.11000/- lasts for 28 days, given by insulin syringe). Prior or concomitant therapy with bisphosphonates may blunt or delay the anabolic response to PTH, but certainly does not abrogate it [7,8]. In addition, treatment with bisphosphonates after a course of PTH may help maintain the gains of PTH therapy [9].

Anabolic steroids

Anabolic androgenic steroids (e.g., testosterone) may increase bone as well as muscle mass. However, high doses produce unacceptable androgenic side effects in many women and thus are best avoided as better options

are available for them. Thus the use of anabolic steroids, except in hypogonadal men, should best be avoided. Testosterone therapy can increase bone mass and improves trabecular architecture in hypogonadal men, where it has been found useful [10].

Thiazides

Thiazides can decrease urinary calcium excretion and increase bone mass in patients with hypercalciuria and may reduce cortical bone loss in normal postmenopausal women and decrease the incidence of hip fractures [11]. Thiazide therapy is particularly appropriate in patients with osteoporosis who have high fasting urinary calcium excretion due to a renal load.

Newer therapeutic regimens

Bisphosphonate

Zoledronic Acid: A recently published Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) pivotal fracture prevention trial involving 7765 postmenopausal women with or without fractures showed 77% reduction in vertebral fractures, 41% reduction in hip fractures and 25% reduction in non-vertebral fractures with 5 mg zoledronic acid IV over 15 minutes once a year compared to placebo [12]. In HORIZON Recurrent Fracture Trial, 2127 hip fracture patients were randomly assigned to receive 5 mg zoledronic acid IV over 15 minutes once a year or placebo starting within 90 days of the fracture [13]. When compared to placebo, zoledronic acid reduced expected deaths after hip fracture by 28% and reduced new clinical fractures by 35%. IV zoledronic acid offers an alternative for individuals who cannot tolerate oral bisphosphonates or who find the dosing regimen more convenient.

Ibandronate: Initially ibandronate was approved for prevention and treatment of osteoporosis in a dose of 2.5 mg daily. Later on dose of 150 mg once a month was approved by USFDA. In 2006, FDA approved intravenous ibandronate for treatment of osteoporosis in the dose of 3 mg over 15-30 minutes every three months [14].

Risedronate: Orally administered risedronate was approved for prevention and treatment of osteoporosis at 5 mg a day in 1998, then 35 mg once a week in 2002 and more recently at 75 mg a day for two days in a month and now FDA approved it as 150 mg once a month therapy [15].

Strontium ranelate

Strontium ranelate is an orally active drug consisting of two atoms of stable strontium and an organic moiety (ranelic acid). In bones, strontium is incorporated, replacing the calcium ions in the hydroxyapatite crystal

lattice over time and increases bone density at least partly because it has a higher atomic weight than calcium. However, it has a unique dual action on bone cells in that it increases bone formation by osteoblasts and simultaneously inhibits bone resorption by osteoclasts. A meta-analysis of phase three trials in past few years concluded that there is reasonable evidence that strontium ranelate is effective for reducing the risk of vertebral fractures and to a lesser extent, non-vertebral fractures [16]. Strontium ranelate appears to be an effective and well-tolerated therapy for women with established osteoporosis. This oral agent has been approved in Europe and other countries for treatment of post-menopausal osteoporosis at the dose of 2 gm/day. It is yet to get US-FDA approval.

Newer therapies requiring further trials

Vitamin K: Exogenous vitamin K is required for the carboxylation of osteocalcin, which in turn allows osteocalcin to bind to hydroxyapatite mineral. A vitamin K2 preparation (menatetrenone) is widely used for the treatment of osteoporosis in Japan. Clinical trial data from Japan suggest that vitamin K supplementation may reduce bone loss and fracture risk [17]. Seven Japanese trials reported fracture data; primarily postmenopausal women with osteoporosis who had used menaquinone. Significant reductions were seen for vertebral, hip and all nonvertebral fractures. This report should be interpreted with some caution, as fracture data are available only in Japanese women, who may have significant dietary differences from other populations. In addition, the magnitude of the fracture risk reductions seems unlikely, as they were far greater than what is seen for other proven therapies, such as bisphosphonates. Based upon the available data, it is therefore presently not recommended to routinely use vitamin K supplementation for the maintenance of skeletal health or the prevention of fractures in high risk individuals. Further larger multicentric trials in different ethnic groups are required.

Tibolone: Tibolone, a synthetic steroid, is a selective tissue estrogenic activity regulator (STEAR), is used for osteoporosis management in some countries. Tibolone has shown to improve bone mineral density by 3-9% in few small studies. In a recent trial, Tibolone was found to be more efficacious when compared to raloxifene in increasing the spine bone mineral density (BMD) [18]. However, the larger LIFT trial, a trial designed to examine the effect of tibolone on vertebral fracture in postmenopausal women, did report a reduction in risk with tibolone. However, this trial was discontinued early due to a possible excess risk of stroke and published data from this trial are not yet available.

Folate/vitamin B₁₂: Combination of folate and vitamin B₁₂ therapy may lower fracture risk in elderly patients with residual hemiplegia after an ischemic stroke [19]. This approach has been studied in 625 elderly Japanese women and men randomly assigned to daily folate (5 mg) and vitamin B₁₂ (1500 µg orally) or placebo. Baseline levels of homocysteine were modestly elevated in both groups, while B₁₂ and folate levels were slightly low. Supplementation reduced the number of hip fractures compared with placebo. Whether the risk reduction is due to the lowering of serum homocysteine or an increase in B₁₂ is not known. In addition, it is not known whether this therapeutic approach will be effective in patients with normal baseline homocysteine, serum B₁₂ and folate concentrations or in other populations.

Growth factors: Growth hormone (GH) and insulin-like growth factor-1 (IGF-1) increase bone collagen and deoxyribonucleic acid (DNA) synthesis in vitro and they stimulate bone growth and osteoblast activity in vivo. Patients with GH deficiency have low bone density. Administration of GH to GH deficient men and women has resulted in improvement in BMD in few studies. The results of trials of GH in women with osteoporosis who did not have GH deficiency have been conflicting, and side effects were common [20]. These conflicting results plus the necessity for administration by injection make it unlikely that GH will become a therapeutic option for patients with osteoporosis who are not GH deficient. IGF-1 therapy does not appear to be effective [21].

Androgens: Because men have higher bone density than women, it has been suggested that treatment with androgens might benefit women with osteoporosis. However, the effect of treatment with androgen plus estrogen on bone mineral density does not appear superior to the effect of estrogen alone and androgen has unwelcome virilizing effects [22]. Androgen therapy for osteoporosis management in women is not recommended. Although testosterone replacement may improve bone density in women with hypopituitarism, available data on the subject is limited and there are no approved testosterone preparations available for use.

Isoflavones: Isoflavones (a type of phytoestrogen) are micronutrient substances that have properties similar to estrogen. Some studies have reported that phytoestrogens have a beneficial effect on markers of bone resorption, BMD and fracture risk in animal models and in postmenopausal women while others have not [23]. There are no randomized trials that assess the effect of isoflavones on fracture as a primary outcome. Based upon available data, isoflavone supplements are not recommended at present, as a strategy to prevent or treat osteoporosis.

Fluoride: There is historical interest in fluoride as an anabolic agent for the treatment of postmenopausal osteoporosis. Although fluoride increases BMD substantially, clinical trials of fluoride have not consistently demonstrated fracture reduction. While some studies demonstrated a decrease in the incidence of new vertebral fracture, others reported no change, or even an increase in nonvertebral fractures [24]. Fluoride impairs bone mineralization, even when the dose is as low as 20 mg daily. Given the availability of other therapies, including parathyroid hormone (anabolic agent), fluoride for the treatment of patients with osteoporosis is not recommended.

Low intensity pulsed ultrasound: A recent trial showed that low intensity pulsed ultrasound increases bone volume, osteoid thickness and mineral apposition rate in the area of fracture healing in patients with a delayed union of the osteotomized fibula [25]. Whether this finding will help in treatment of osteoporotic fractures remains to be seen.

Some other compounds are also undergoing evaluation for potential antiresorptive use in prevention and treatment of osteoporosis including c-Src kinase inhibitors (Src, a non-receptor tyrosine kinase, is an important regulator of osteoclast-mediated resorption), statins and chloride channel inhibitors. Chloride channel activity is essential for osteoclast function. Consequently, inhibition of the osteoclastic chloride channel should prevent bone resorption. A study on ovariectomized mice revealed that a chloride channel inhibitor inhibits bone resorption without affecting bone formation. This study indicates that chloride channel inhibitors are highly promising for treatment of osteoporosis.

Emerging novel therapies

Denosumab

Denosumab is a fully humanized mouse monoclonal antibody directed against receptor activator of nuclear factor-kappa B ligand (RANKL). RANKL, a member of the turnover necrosis factor (TNF) super-family of ligands and receptors, is essential for the function of bone-resorbing osteoclasts; RANKL accelerates osteoclastogenesis when it binds to its receptor, RANK, but is blocked by osteoprotegerin, which is produced by osteoblasts. Denosumab functions like osteoprotegerin to limit RANKL activity and thereby reduces osteoclast numbers and activity. Concluded phase two trials have shown efficacy in treatment of osteoporosis and phase three trials are rapidly concluding for use in patients with post-menopausal osteoporosis, male osteoporosis, glucocorticoid-induced osteoporosis and rheumatoid arthritis. In a just concluded trial, Denosumab as subcutaneous injection in a dose of 60 mg every six

Table 1**Drugs approved by US-FDA for treatment of osteoporosis**

Drug	Dose	Spine BMD gain (%) / fracture reduction (%)
Antiresorptive		
Bisphosphonate		
Alendronate	10 mg/day or 70 mg/week orally	6-8 / 40-50
Risedronate	5 mg/day or 35 mg/week orally	
Ibandronate	2.5 mg/day or 150 mg/month orally or 3 mg intravenously x 3 monthly	5-7 / ~ 40
Zoledronic acid	5 mg intravenously x 12 monthly	
Raloxifene(SERM)	60 mg/day orally	1.5-3 / 30-50
Estrogen	Variable doses and routes (oral and transdermal)	3-5 / ~ 35
Calcitonin	200 IU/day intranasally or 50-100 IU/day intramuscular	1-1.5 / 20-30
Anabolic		
Teriparatide	20 µg/day subcutaneously (For 12-18 months)	13-15 / 60-70

months, has shown increased BMD after 12 months at the lumbar spine by 3.0 to 6.7% and at total hip by 1.9 to 3.6% [26]. These results are comparable to effects of alendronate therapy. An important issue with denosumab is that RANKL functions within the immune system in addition to regulating osteoclastogenesis, therefore raising concern about potential infectious complications. In the trial described above, there were six cases of serious adverse events of infections in the denosumab group (diverticulitis, pneumonia, atypical pneumonia, and labyrinthitis).

Sclerostin antibody

Sclerostin is a protein produced by sclerosteosis (SOST) gene almost exclusively in osteocytes. This protein normally inhibits bone formation by preventing interactions of Wnt proteins with the (LRP-5/6) receptor on the plasma membrane of osteoblasts and osteoblast precursors on the bone surfaces, thereby decreasing osteoblast recruitment and activation. A new monoclonal antibody to sclerostin inhibits sclerostin activity, thereby up regulating Wnt signaling pathway and activating osteoblast recruitment and activity. Increased osteoblastic activity leads to increased bone formation similar to that as seen with teriparatide. In animal models, administration of sclerostin antibodies has shown to increase bone mass [27]. Further trials are underway.

Cathepsin K inhibitors

Cathepsin K is a cysteine protease of the papain family that is abundantly and selectively expressed in osteoclast. This is a major protease that degrades type I collagen and other proteins in bone matrix during bone resorption. So inhibition of cathepsin K could potentially be an effective method to prevent osteoporosis. Several phase 2 trials with cathepsin K inhibitors have been completed, demonstrating mild to moderate anti-resorptive effect [27,28].

Integrin antagonists

Integrins mediate the adhesion of osteoclasts to the bone surface, an important initial step for bone resorption. In a multicenter, randomized, double blind, placebo-controlled, 12-month study, 227 women (average age 63 year) with low lumbar spine or femoral neck BMD were randomly assigned to receive 100 or 400 mg L-000845704 (an alpha V beta 3 integrin antagonist) [29]. Only 200 mg L-000845704 twice daily significantly increased BMD at the hip and femoral neck. L-000845704 was generally well tolerated. This data suggests that the alpha V beta 3 integrin antagonist L-000845704 could be developed as an effective antiresorptive agent for treatment of osteoporosis.

Calcium sensing receptor antagonists

Administration of calcium sensing receptor (CaSR) antagonists leads to a transient rise in endogenous parathyroid hormone, similar to intermittently administered exogenous parathyroid hormone. In animal model administration of CaSR antagonist caused robust, rapid and transient increase in serum PTH levels when administered either IV or orally [27,30]. These data describe a representative compound of a novel chemical class than previously described allosteric modulators that offer a new avenue for the development of improved osteoanabolic treatment of osteoporosis.

With the newer regimens and shortly to be available new class of drugs for treatment of osteoporosis, there will be expansion of available therapeutic armamentarium and thus allow clinicians to better individualize patient treatment.

Conflicts of Interest

None identified

References

1. Reid IR, Bolland MJ, Grey A. Effect of calcium supplementation on hip fractures. *Osteoporos Int* 2008; 19: 1119-23.
2. Ish-Shalom S, Segal E, Salganik T, Raz B, Bromberg IL, Vieth RL. Comparison of daily, weekly, and monthly vitamin D3 in ethanol dosing protocols for two months in elderly hip fracture patients. *J Clin Endocrinol Metab* 2008; 93: 3430-5.

3. Bone HG, Hosking D, Devogelaer JP. Ten years' experience with alendronate for osteoporosis in postmenopausal women. *N Engl J Med* 2004; 350: 1189-99.
4. Anderson GL, Limacher M, Assaf AR. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: the Women's Health Initiative randomized controlled trial. *JAMA* 2004; 291: 1701-12.
5. Greenspan SL, Emkey RD, Bone HG. 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.
6. Chesnut 3rd CH, Silverman S, Andriano K. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. *Am J Med* 2000; 109: 267-76.
7. Black DM, Greenspan SL, Ensrud KE. The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. *N Engl J Med* 2003; 349: 1207-15.
8. Cosman F, Nieves J, Zion M, Woelfert L, Luckey M, Lindsay R. Daily and cyclic parathyroid hormone in women receiving alendronate. *N Engl J Med* 2005; 353: 566-75.
9. Black DM, Bilezikian JP, Ensrud KE. One year of alendronate after one year of parathyroid hormone (1-34) for osteoporosis. *N Engl J Med* 2005; 353: 555-65.
10. Kenny AM, Prestwood KM, Gruman CA, Fabregas G, Biskup B, Mansoor G. Effects of transdermal testosterone on bone and muscle in older men with low bioavailable testosterone levels. *J Gerontol A Biol Sci Med Sci* 2001; 56: 266-72.
11. Reid IR, Ames RW, Orr-Walker BJ. Hydrochlorothiazide reduces loss of cortical bone in normal postmenopausal women: a randomized controlled trial. *Am J Med* 2000; 109: 362-70.
12. Black DM, Delmas PD, Eastell R. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; 356: 1809.
13. Lyles KW, Colon-Emeric CS, Magaziner JS. Zoledronic acid and clinical fractures and mortality after hip fracture. *N Engl J Med* 2007; 357: 1799.
14. Delmas PD, Adami S, Strugala C. Intravenous ibandronate injections in postmenopausal women with osteoporosis: one-year results from the dosing intravenous administration study. *Arthritis Rheum* 2006; 54: 1838.
15. Delmas PD, Benhamou CL, Man Z. Monthly dosing of 75 mg risenedronate on 2 consecutive days a month: Efficacy and safety results. *Osteoporos Int* 2008; 19: 1039-45.
16. O'donnell S, Cranney A, Wells G, Adachi JD, Reginster JY. Strontium ranelate for preventing and treating postmenopausal osteoporosis. *Cochrane Database Syst Rev* 2006; 3: CD005326.
17. Cockayne S, Adamson J, Lanham-New S, Shearer MJ, Gilbody S, Torgerson DJ. Vitamin K and the prevention of fractures: systematic review and meta-analysis of randomized controlled trials. *Arch Intern Med* 2006; 166: 1256.
18. Delmas PD, Davis SR, Hensen J. Effects of tibolone and raloxifene on bone mineral density in osteopenic postmenopausal women. *Osteoporos Int* 2008; 19: 1153-60.
19. Sato Y, Honda Y, Iwamoto J, Tomohiro K, Satoh K. Effect of folate and mecobalamin on hip fractures in patients with stroke: a randomized controlled trial. *JAMA* 2005; 293: 1082.
20. Holloway L, Butterfield G, Hintz RL, Gesundheit N, Marcus R. Effects of recombinant human growth hormone on metabolic indices, body composition and bone turnover in healthy elderly women. *J Clin Endocrinol Metab* 1994; 79: 470.
21. Friedlander AL, Butterfield GE, Moynihan S. One year of insulin-like growth factor I treatment does not affect bone density, body composition, or psychological measures in postmenopausal women. *J Clin Endocrinol Metab* 2001; 86: 1496.
22. Erdtsieck RJ, Van Kujik C, Birkenhager-Frenkel DH. Course of bone mass during and after hormonal replacement therapy with and without addition of nandrolone decanoate. *J Bone Miner Res* 1994; 9: 277.
23. Alexandersen P, Toussaint A, Christiansen C. Ipriflavone in the treatment of postmenopausal osteoporosis: a randomized controlled trial. *JAMA* 2001; 285: 1482-8.
24. Reid IR, Cundy T, Grey AB. Addition of monofluorophosphate to estrogen therapy in postmenopausal osteoporosis: a randomized controlled trial. *J Clin Endocrinol Metab* 2007; 92: 2446.
25. Rutten S, Nolte PA, Korstjens CM, van Duin MA, Klein-Nulend J. Low-intensity pulsed ultrasound increases bone volume, osteoid thickness and mineral apposition rate in the area of fracture healing in patients with a delayed union of the osteotomized fibula. *Bone* 2008; 43: 348-54.
26. McClung MR, Lewiecki EM, Cohen SB. Denosumab in postmenopausal women with low bone mineral density. *N Engl J Med* 2006; 354: 821.
27. Grey A. Emerging pharmacologic therapies for osteoporosis. *Expert Opin Emerg Drugs*. 2007;12: 493-508.
28. Tavares FX, Boncek V, Deaton DN. Design of potent, selective, and orally bioavailable inhibitors of cysteine protease cathepsin K. *J Med Chem* 2004; 47: 588.
29. Murphy MG, Cerchio K, Stoch SA. Effect of L-000845704, an alphaVbeta3 integrin antagonist, on markers of bone turnover and bone mineral density in postmenopausal osteoporotic women. *J Clin Endocrinol Metab* 2005; 90: 2022.
30. Arey BJ, Seethala R, Ma Z. A novel calcium-sensing receptor antagonist transiently stimulates parathyroid hormone secretion in vivo. *Endocrinology* 2005; 146: 2015.