New approaches to pharmacological treatment of osteoporosis

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Abstract Osteoporosis has been recognized as a major public health problem for less than two decades. The increasing incidence of fragility fractures, such as vertebral, hip, and wrist fractures, first became apparent from epidemiological studies in the early and mid-1980s, when effective treatment was virtually unavailable. Pharmacological therapies that effectively reduce the number of fractures by improving bone mass are now available widely in countries around the world. Most current agents inhibit bone loss by reducing bone resorption, but emerging therapies may increase bone mass by directly promoting bone formation — as is the case with parathyroid hormone. Current treatment alternatives include bisphosphonates, calcitonin, and selective estrogen receptor modulators, but sufficient calcium and vitamin D are a prerequisite. The availability of evidence-based data that show reductions in the incidence of fractures of 30–50% during treatment has been a major step forward in the pharmacological prevention of fractures. With all agents, fracture reduction is most pronounced for vertebral fracture in high-risk individuals; alendronate and risedronate also may protect against hip fracture in the elderly. New approaches to pharmacological treatment will include further development of existing drugs, especially with regard to tolerance and frequency of dosing. New avenues for targeting the condition will emerge as our knowledge of the regulatory mechanisms of bone remodelling increases, although issues of tissue specificity may be difficult to solve. In the long term, information gained through knowledge of bone genetics may be used to adapt pharmacological treatments more precisely to each individual.

Keywords Osteoporosis/drug therapy; Osteoporosis, Postmenopausal/drug therapy; Fractures/pathology; Osteoclasts/drug effects/enzymology; Osteoblasts/drug effects; Bone and bones/physiopathology; Calcium, Dietary/therapeutic use; Vitamin D/therapeutic use; Diphosphonates/therapeutic use; Calcitonin/therapeutic use; Norpregnenes/therapeutic use; Estrogen replacement therapy; Parathyroid hormones/physiology; Organometallic compounds//therapeutic use (*source: MeSH, NLM*).
Mots clés Ostéoporose/chimiothérapie; Ostéoporose postménopause/chimiothérapie; Fracture/anatomie pathologique; Ostéoclaste/action des produits chimiques/enzymologie; Ostéoblaste/action des produits chimiques; Os/physiopathologie; Calcium alimentaire/usage thérapeutique; Vitamine D/usage thérapeutique; Diphosphonates/usage thérapeutique; Calcitonine/usage thérapeutique; Norprégnènes/usage thérapeutique; Oestrogénothérapie substitutive; Hormones parathyroïdiennes/physiologie; Organométalliques, Composés/usage thérapeutique (*source: MeSH, INSERM*).
Palabras clave Osteoporosis/quimioterapia; Osteoporosis postmenopáusica/quimioterapia; Fracturas/patología; Osteoclastos/efectos de drogas; Osteoblastos/efectos de drogas/enzimología; Calcio en la dieta/uso terapéutico; Vitamina D/uso terapéutico; Huesos/fisiopatología; Difosfonatos/uso terapéutico; Calcitonina/uso terapéutico; Norpregnenos/uso terapéutico; Terapia de reemplazo de estrógeno; Hormonas paratiroídeas/fisiología; Compuestos organometalicos/uso terapéutico (*fuente: DeCS, BIREME*).

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Introduction

Osteoporosis is structural failure of the skeleton that causes an increased risk of fracture. Low bone mass and microarchitectural deterioration of bone tissue increase bone fragility, which means that fractures can occur after low-energy traumas. Such fractures are associated with mortality and with significant short- and long-term morbidity. The management of osteoporosis must target all aspects of the condition: bone mass should be maximized; fractures should be prevented; and people who have already sustained a fracture should be rehabilitated to minimize associated pain, limitation of activities, and restriction of participation in society. Pharmacological treatments act on bone and have effects on its mass, strength, and turnover.

Pharmacological treatments that primarily and effectively reduce bone loss and fracture risk have become available in the last few decades. The role of estrogen for maintenance of bone integrity was recognized early on, and hormone replacement therapy was recommended to prevent osteoporosis. Hormone replacement therapy is non-specific, however, and with evidence of its undesirable side-effects and low compliance rates, the search for more potent and specific treatments with large effects on bone mass resulted in the development of direct anti-resorptive agents, including the bisphosphonates and selective estrogen receptor modulators.

This paper outlines the underlying bone biology and describes the therapies currently used to treat osteoporosis. It also looks at new approaches to the use of current treatments and the development of new agents to prevent development of the condition.

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Risk factors for osteoporosis and fracture

Low bone mass is a major independent risk factor for fracture, along with a number of other risk factors (of variable importance) that relate to the impact and frequency of trauma and to protective mechanisms. It is essential to recognize that the risk factors for developing osteoporosis, i.e. low bone mass, and the risk factors for sustaining a fracture are not identical, but that bone fragility is a very important factor that enhances the risk of fracture after low energy trauma. The etiology of idiopathic osteoporosis is similarly multifactorial: apart from its relation with age and sex, it also is related strongly to genetic and environmental factors. As a person ages, resorbed bone is replaced incompletely, which leads to a net loss of bone; osteoporosis is defined as a bone mineral density that is 2.5 standard deviations less than the mean value for young adults (*1*). Probably the two most important ways to maintain a bone mass above a dangerous fracture threshold are to attain a high peak bone mass in young adulthood and to have a low rate of loss during ageing.

Bone biology — systemic and local regulation of bone turnover

Current pharmacological treatments for osteoporosis were developed on the basis of existing knowledge of basic bone biology, while the development of novel therapies will rely on the exploration of fundamental regulatory mechanisms. The balance between bone resorption and bone formation is maintained through a complex regulatory system of systemic and local factors that act on bone cells, such as calcium-regulating hormones, sex hormones, growth factors, and cytokines (Table 1). The competence of bone cells and the number of active cells determines the production of bone matrix proteins, while other incompletely understood intrinsic mechanisms determine mineralization and microstructure formation.

Resorption of bone at a specific site may be induced by microdamage, but the initiating event in the process of osteoclastic activation is not understood. After activation, osteoclasts cause a local decrease in pH, which precipitates the dissolution of mineral. Exposure of the matrix permits enzymatic degradation of the collagenous structure. The signals responsible for termination of bone resorption and initiation of bone formation (coupling) are not well understood; however, evidence suggests that the liberation of components of the matrix-embedded, insulin-like growth factor (IGF) system — IGF-I, IGF-II, and their binding proteins — may induce this shift (*2*). Other putative coupling factors include cytokines, of which the interleukins IL-1, IL-6, IL-11, transforming growth factor-β, and tumour necrosis factor-α seem to be involved most closely in the regulation of bone turnover. Tight coupling between resorption and formation is needed to maintain bone mass and preserve the structural integrity of the bone. Incomplete filling of resorptive cavities results in the net loss of bone that is characteristic of osteoporosis.

Pharmacological treatment

In general, pharmacological agents either decrease bone resorption to produce secondary gains in bone mass or are anabolic and produce direct increases in bone mass. Ideally, such drugs also should increase bone strength and bone quality. As the turnover of bone is slow, the time between starting treatment and assessing its effect on bone mass or fracture takes several years. Because this makes it difficult to show the effect of treatments on the dichotomous and uncommon key outcome of fracture, the continuous variable bone mass is often used as a surrogate measure. An increasing number of randomized controlled trials of several anti-osteoporotic drugs have fracture as an endpoint, however, and show reductions in the incidence of fractures within 1–3 years.

In addition to estrogen, drugs with specific anti-resorptive actions are available for the treatment of osteoporosis, including bisphosphonates, calcitonin, and selective estrogen receptor modulators. Furthermore, calcium and vitamin D act on bone by decreasing resorption, while calcium also is regarded as an essential building block for bone.

Table 1. **Systemic and local regulators of bone turnover**

Hormones	Local factors
Polypeptide hormones	**Polypeptide growth factors**
Parathyroid hormone	Insulin-like growth factor
Calcitonin	Transforming growth factor-β family of peptides (bone morphogenic proteins, inhibins, activins)
Insulin	Fibroblast growth factors
Growth hormone	Platelet-derived growth factor
Steroid hormones	**Cytokines from the immune and haematological system**
1,25-dihydroxyvitamin D_3	Tumour necrosis factor (osteoclast-differentiating factor, receptor activator of nuclear factor κB ligand, osteoprotegerin)
Sex steroids	γ-Interferon, colony-stimulating factor, interleukins
Thyroid hormones	**Other factors**
	Prostaglandins

Calcium and vitamin D

Calcium and vitamin D in combination is the accepted baseline treatment for osteoporosis and also is used as a preventive measure, particularly for frail elderly patients. After three years of treatment with calcium (1200 mg) and vitamin D (20 μg (800 IU)), the incidence of new hip and non-vertebral fractures in elderly patients was lower than in patients who did not receive such treatment and a significant benefit was seen after 18 months (*3*). Vitamin D therapy may have additional benefits for very elderly patients, because it increases muscle strength and thus may reduce the number of falls and possibly of fractures (*4, 5*).

Bisphosphonates

Bisphosphonates are derived chemically from pyrophosphates — compounds that inhibit precipitation of calcium carbonate. They are characterized by two carbon–phosphorus bonds that, when located on the same carbon atom (i.e., *gem*), allow large variations in side-chains. The different side-chain combinations give each compound specific physiological and biochemical properties.

Bisphosphonates have anti-resorptive activity and little effect on other organ systems. They act on bone by binding to hydroxyapatite and by inhibiting activation of osteoclasts (*6*). Nitrogen-containing bisphosphonates inhibit the mevalonate metabolic pathway, while bisphosphonates that do not contain nitrogen are metabolized in the cell into cytotoxic analogues of adenosine triphosphate (Box 1). The plasma half-life of bisphosphonates is very short, but the half-life of bisphosphonates deposited in bone is probably up to 10 years — and could be longer (*6*).

In large, randomized, controlled trials, alendronate reduced vertebral and non-vertebral fractures (*7, 8*). Alendronate is most efficient at reducing fracture in people at highest risk of fracture — that is, women with at least one prevalent vertebral fracture or with a measured bone density that confirms osteoporosis. Rates of symptomatic vertebral fractures, which often are encountered in clinical practice, were reduced by 28–36% over 3–4 years of treatment, while rates of asymptomatic and radiographically identified vertebral deformities were reduced by 44–47% and of hip fracture by 51%. Risedronate similarly reduced the rate of vertebral fractures by about 40–49% over three years (*9, 10*). A study specifically designed to evaluate the effect of risedronate on the incidence of hip fracture included elderly women on the basis of risk factors alone or a combination of risk factors and bone mass density. Interestingly, hip fractures were reduced significantly (by 49%) only in women with low bone-mass density at the start of therapy; a non-significant reduction was seen in women included on the basis of risk factors alone (*11*).

Bisphosphonates are absorbed poorly from the gastrointestinal tract, which complicates their oral administration and has prompted the development of new dosing regimens, as well as new compounds through side-chain substitutions. Oral administration of alendronate and risedronate requires fasting before and immediately after the drug is taken. Alendronate, in particular, has been associated with severe gastric side-effects because it produces oesophageal erosions. In a number of countries, the availability of preparations that contain the total weekly dose of alendronate or risedronate in a single tablet has meant that patients can choose to take their treatment as one tablet taken once a week. The effect on bone mineral density of one weekly dose is similar to the effect of the dose taken spread throughout the week, and the fracture effect is assumed to be comparable with reductions seen in earlier studies (*12, 13*). Despite the high dose contained in the single tablet, the risk of adverse gastrointestinal events may be lower than with once-daily tablets. This simplified dosing regimen should increase compliance, which would be favourable in terms of total effect.

The difficulty with optimizing the effect of orally administered bisphosphonates because of their low bioavailability and gastrointestinal side-effects can also be overcome by administering them intravenously. Intravenous administration of bisphosphonates of lower potency does require infusion, however, and so this is less useful for the widespread treatment of outpatients. The use of a more potent aminobisphosphonate, ibandronate, administered as a bolus intravenous injection every three months, led to increases in bone mineral density of up to 5.2% for the lumbar spine and up to 2.9% for the total hip after 12 months compared with patients who received placebo (*14*). Similarly, a recent report indicated a consistent increase in bone mineral density in the lumbar spine and hip after either two doses per year or a single annual dose of zolendronic acid — the currently most potent bisphosphonate — in postmenopausal women with osteoporosis (*15*). The results are promising and would enable the treatment of patients who are unable to comply with oral bisphosphonate therapy because of frailty, severe comorbidity, or gastric intolerance. Data on fracture rates are pending, and zolendronic acid is not yet available for routine use.

Box 1. **Examples of bisphosphonates**

Nitrogen-containing bisphosphonates
- Alendronate
- Risedronate
- Ibandronate
- Zolendronate

Non-nitrogen-containing bisphosphonates
- Etidronate
- Tiludronate
- Clodronate

Calcitonin

Calcitonin acts as an endogenous inhibitor of bone resorption by decreasing osteoclast formation. It is available for delivery as a subcutaneous injection or nasal spray; both formulations are developed from salmon calcitonin, which is about 10 times more potent than naturally produced human calcitonin. Several studies have shown positive effects on bone mineral density in postmenopausal women, but the effect on fractures has been less well documented. In a recent report, new vertebral fractures were reduced by 33% in postmenopausal women after salmon calcitonin was given at a dose of 200 IU daily, despite the effect on lumbar bone mineral density being small (*16*). This was interpreted as a quality effect on bone trabeculae beyond the effect on bone mineral density. As a

desirable additional effect, calcitonin has been noted to reduce the pain of clinical vertebral fractures (*17*).

Selective estrogen receptor modulators

Selective estrogen receptor modulators, such as raloxifene, block conformational changes of the estrogen receptor. In postmenopausal women treated with raloxifene, the incidence of vertebral fractures was reduced by 30% over three years, but no effect was seen on the incidence of non-vertebral fractures (*18*). In addition, other beneficial effects have been seen: a significant (72%) decrease in new cases of breast cancer (*19*) and a significant reduction in the incidence of cardiovascular events in women who had increased cardiovascular risk (*20*).

Estrogen replacement therapy

Treatment of women with osteoporosis with estrogen replacement therapy to prevent fracture has been controversial. Large studies to evaluate the effect on the incidence of fracture, particularly in the elderly, have been lacking, and the indication for its efficacy relies on observational studies. The Women's Health Initiative trial on estrogen replacement therapy was the first large-scale, randomized, controlled study of healthy women aged 50–79 years (*21*). The incidence of osteoporotic fractures — a secondary endpoint of the study — was reduced by 24%, and the risk reduction for hip and vertebral fractures was 34%. Long-term side-effects, particularly development of breast cancer, and the long-term absence of benefits for cardiovascular events limit their use. The primary reason for using estrogen replacement therapy therefore is to eliminate climacteric symptoms in women soon after menopause: the bone-sparing effect should be regarded as an added benefit, and the treatment rarely should exceed five years.

Tibolone

Tibolone is a synthetic steroid with estrogenic, androgenic, and gestagenic properties, which exerts its effect by binding to the estrogen receptor. Tibolone relieves climacteric symptoms without causing menstrual bleeding and with less breast tenderness than is caused by hormone replacement therapy. After two years of treatment with tibolone in early postmenopausal women, the bone density response was similar to that after estrogen replacement therapy (*22, 23*), while in a head-to-head trial, tibolone induced a dose-dependent increase in bone mineral density of the lumbar spine, although this increase was smaller than with conventional continuous hormone replacement therapy (*24*). The change in bone mineral density in the hip was similar but did not reach significance (*24*). No data are available on fracture prevention, so from an evidence-based perspective, tibolone cannot be recommended for the treatment of osteoporosis.

Parathyroid hormone

Parathyroid hormone is a single-chain peptide consisting of 84 amino acids. The sequence and structure is well defined, and the *N*-terminal 1–34 amino acid residues are essential for the hormone's activity. The physiological function of parathyroid hormone is to maintain extracellular calcium levels. It acts either directly on target cells or indirectly through the synthesis of 1,25-dihydroxyvitamin D_3. Evidence suggests that parathyroid hormone has a dual action on bone, with both osteoblasts and osteoclasts being responsive to parathyroid hormone. The resorptive effect predominates when levels of parathyroid hormone are elevated continuously, but an anabolic effect on bone is seen with intermittent dosing.

Use of the anabolic properties of parathyroid hormone on bone has been seen as an attractive way of gaining larger increases in bone mass than are possible with anti-resorptive agents. Parathyroid hormone has been shown primarily to increase the cancellous or trabecular bone, so the most pronounced effects are seen in the bone mineral density of the spine (*25*). A smaller but clear effect is also seen on the endosteal surface of cortical bone, however, as increased breaking strength has been seen in animal studies (*26, 27*).

Recombinant human parathyroid hormone given as a daily subcutaneous injection has been evaluated in osteoporosis. Postmenopausal women with prevalent vertebral fractures who received 20 μg or 40 μg of recombinant human parathyroid hormone 1–34 experienced 65–69% reductions in the incidence of new vertebral fractures and 53–54% reductions in non-vertebral fractures over 21 months (*28*). Dose-dependent increases in the bone mineral densities of the spine and femoral neck of 9–13 % and 6–9%, respectively, were seen. Other studies have shown marked increases in bone mineral densities, predominantly in the spine, and have suggested reductions in the incidence of vertebral fractures, particularly when parathyroid hormone has been combined with agents that reduce bone resorption (*29, 30*). Furthermore, during a 14-month study of women with osteoporosis, recombinant human parathyroid hormone 1–34 increased the bone mineral densities of the spine and the hip significantly more than daily alendronate (*31*).

Anabolic agents to counteract severe bone loss in osteoporosis are highly desirable. Treatment with parathyroid hormone produces incremental increases in bone mineral density, particularly of cancellous bone in the vertebrae, even after short periods of treatment. Parathyroid hormone seems to be a new treatment option, especially for severe cases of osteoporosis that are unresponsive to other agents or possibly in patients in whom side-effects prohibit the use of other agents. Since patients who take parathyroid hormone need to be monitored more closely because of the risk of hypercalcaemia, and as such treatment will be very costly, cyclic combination therapy with parathyroid hormone and, for example, a bisphosphonate may be a future alternative for long-term treatment. Parathyroid hormone is licensed in only a few countries at present.

Strontium ranelate

Strontium ranelate has been shown to inhibit bone resorption without depressing bone formation in both in vitro and animal studies (*32, 33*). Strontium is adsorbed onto the bone surface and increases bone strength by being incorporated in a dose-dependent manner into bone tissue to change the crystal structure but without altering mineralization (*34*).

In a randomized controlled trial of postmenopausal women with osteoporosis, treatment with strontium ranelate

increased bone mineral density in a dose-dependent way by 1.4–3.0% per year compared with placebo (*35*). New vertebral fractures were reduced by 44% after two years in women on the highest dose (2 g). The treatment was well tolerated, and the larger dose was suggested for clinical use. The use of strontium, normally regarded as a trace element, may offer an alternative way of decreasing bone resorption; however, at present, strontium is not approved for use.

Growth factors, cathepsin K, cytokines, and other approaches

Growth factors

Osteoclasts are unique in their ability to dissolve and degrade bone tissue. This is achieved through the production of numerous substances involved in mineral dissolution and enzymatic degradation of the matrix, which may be targets for prospective drug research, in addition to factors that influence osteoclast development.

Identification of factors that act on receptors for osteoclast attachment or function — such as $\alpha_v\beta_3$ integrin, receptor activator of nuclear factor κB ligand (RANKL), or the soluble ligand osteoprotegerin — may allow the development of receptor antagonists. Clinical testing of osteoprotegerin indicates a positive effect on bone mineral density in postmenopausal women (*36*).

Cathepsin K

Degradation of the bone matrix is mediated by cathepsin K, an osteoclast protease that appears to act specifically on bone collagen (*37*). Animal models confirm the important effect of cathepsin K, and deletion of the cathepsin K gene results in osteopetrotic bone in mice (*38*). An inhibitor of cathepsin K may be useful as an anti-resorptive drug.

Cytokines

Recent developments in knowledge about cell differentiation and cell activity show that cytokines are important regulators at the local level. In addition, molecular biology has provided novel insights into intracellular signalling and cell-to-cell communication between osteoblasts and osteoclasts. Most cytokines are implicated as enhancers of osteoclast activity and, subsequently, of bone resorption. Blockade of cytokine activity already has gained success in the treatment of rheumatoid arthritis with anti-tumour necrosis factor-α, and this may have additional effects on bone turnover, since tumour necrosis factor-α is one of the more important cytokines that modify bone resorption. Levels of bone resorption markers decrease significantly in patients with rheumatoid arthritis treated with infliximab (*39*). This may allow the development of inhibitors of other bone-active cytokines, such as IL-1 or IL-6. The relative non-specificity and subsequent effects on other organs, however, may limit their usefulness.

Other approaches

Future approaches may include genetic modification and pharmacogenetic methods developed as a result of our still-increasing knowledge of the genetics of bone diseases. A number of genes have been identified as possibly being associated with osteoporosis and fracture, although results are inconsistent. Variations in the collagen, estrogen receptor and vitamin D receptor genes merit mentioning as they have been associated with bone mineral density and fracture in elderly women, with implications of functional importance for the collagen polymorphism (*40–42*).

Conclusion

Osteoporosis and fragility fractures are a problem worldwide, and increasing numbers of people are at risk of fracture because of the demographic changes caused by people reaching more advanced ages than ever before. Osteoporosis is a multifactorial condition, and its prevention and treatment must involve all possible options — from rather simple fall prevention measures to the use of pharmacological agents with complex mechanisms of action.

Effective pharmacological treatments are available in most countries. Evidence-based data on the efficacy of drugs in preventing fractures support their use, but after those in need of treatment are identified accurately. All agents are most effective in the patients at highest risk — that is, patients with verified or established osteoporosis — and treatment should be instigated alongside public health measures. Pharmacological treatments are costly (with the exception of the combination of calcium and vitamin D) and exceed the economic resources of patients in many countries. Often patients in need are undertreated or deprived of effective treatment, therefore, and this is an issue that needs to be considered by health providers, as well as the pharmaceutical industry.

Future approaches to pharmacological treatment will rely on further development of currently available agents, such as bisphosphonates, in terms of potency and dosing. Our increasing knowledge of the mechanisms that regulate bone-cell activity will provide sources for potential new therapeutic strategies. Future approaches thus may include local regulators, such as cytokines (which are essential in bone metabolism), modification of hormone receptors (and other receptors), and pharmacogenetics. From a global perspective, treatment must be affordable and accessible to most of those in need, but newly developed drugs tend to be costly. ■

Conflicts of interest: none declared.

Résumé

Nouvelles modalités de traitement pharmacologique de l'ostéoporose

Il y a moins de vingt ans que l'ostéoporose est considérée comme un problème de santé publique important. L'incidence croissante des fractures par fragilité osseuse, telles les fractures vertébrales, de la hanche et du poignet, est apparue pour la première fois dans des études épidémiologiques effectuées au début et au milieu des années 80, alors qu'on ne disposait pratiquement d'aucun traitement. Des traitements pharmacologiques qui réduisent avec succès le nombre de fractures en reconstituant la masse osseuse sont aujourd'hui largement disponibles dans le monde entier. La plupart des produits actuels réduisent la perte osseuse en inhibant la résorption osseuse, mais les nouveaux traitements pourraient permettre d'accroître véritablement la masse osseuse en favorisant directement l'ossification - comme c'est le cas avec l'hormone parathyroïdienne. Les autres possibilités actuelles de traitement font appel aux bisphosphonates, à la calcitonine, aux modultateurs sélectifs des récepteurs des oestrogènes, mais des apports suffisants en calcium et en vitamine D sont une condition préalable. Le fait de disposer de données factuelles montrant des réductions de 30 à 50 % de l'incidence des fractures au cours du traitement a constitué un grand pas en avant pour la prévention pharmacologique des fractures. Avec tous ces produits, la diminution du nombre de fractures est particulièrement marquée pour les fractures vertébrales chez les sujets à haut risque ; l'alendronate et le risédronate protègent peut-être également contre la fracture de la hanche chez la personne âgée. Les nouvelles stratégies de traitement pharmacologique comprendront le perfectionnement des médicaments existants, surtout en ce qui concerne la tolérance et la fréquence des prises. De nouvelles possibilités de cibler cette maladie apparaîtront au fur et à mesure que notre connaissance des mécanismes régulateurs du remodelage osseux se précisera, même si les problèmes de spécificité tissulaire peuvent être difficiles à résoudre. A terme, on utilisera peut-être ce que l'on sait de la génétique osseuse pour adapter plus précisément les traitements pharmacologiques à chaque individu.

Resumen

Nuevos enfoques del tratamiento farmacológico de la osteoporosis

La osteoporosis sólo ha sido reconocida como un importante problema de salud pública hace menos de dos décadas. El aumento de la incidencia de fracturas osteoporóticas, como las fracturas vertebrales, de la cadera y del antebrazo, se evidenció por primera vez en estudios epidemiológicos realizados a principios y mediados de los años ochenta, cuando prácticamente no existían tratamientos eficaces. En la actualidad hay en varios países del mundo una amplia disponibilidad de tratamientos farmacológicos que reducen eficazmente el número de fracturas gracias a que mejoran la masa ósea. La mayoría de los fármacos actuales reducen la pérdida ósea inhibiendo la resorción ósea, pero empiezan a aparecer tratamientos que pueden aumentar verdaderamente la masa ósea, gracias a un aumento directo de la formación de hueso, como ocurre con la hormona paratiroidea. Las alternativas terapéuticas actuales incluyen los bisfosfonatos, la calcitonina y los moduladores selectivos de los receptores de estrógenos, pero la disponibilidad de calcio y vitamina D suficientes es un requisito previo de todas ellas. La existencia de datos objetivos que muestran reducciones de la incidencia de fracturas del orden del 30% al 50% durante el tratamiento ha representado un gran paso adelante en la prevención farmacológica de las fracturas. Con cualquiera de los fármacos, las mayores reducciones corresponden a las fracturas vertebrales en individuos con alto riesgo; el alendronato y el risedronato también pueden conferir protección frente a las fracturas de cadera en los ancianos. Los nuevos enfoques farmacoterapéuticos incluirán el perfeccionamiento de los fármacos ya existentes, sobre todo en lo que se refiere a su tolerancia y a la frecuencia de las tomas. A medida que aumenten nuestros conocimientos sobre los mecanismos reguladores de la remodelación ósea, se encontrarán nuevas dianas terapéuticas de la enfermedad, aunque podría haber dificultades para resolver los problemas de histoespecificidad. A largo plazo, la información aportada por la genética ósea podrá utilizarse para adaptar mejor los tratamientos farmacológicos a cada individuo.

References

1. World Health Organization. *Assessment of osteoporotic fracture risk and its role in screening for postmenopausal osteoporosis.* Geneva: WHO; 1994.
2. Hayden JM, Mohan S, Baylink DJ. The insulin-like growth factor system and the coupling of formation to resorption. *Bone* 1995;17 2 Suppl: 93S-8S.
3. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S, et al. Vitamin D3 and calcium to prevent hip fractures in the elderly women. *New England Journal of Medicine* 1992;327:1637-42.
4. Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C, et al. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. *Journal of Bone and Mineral Research* 2003;18:343-51.
5. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. *BMJ* 2003;326:469.
6. Fleisch H. *Bisphosphonates in bone disease. From the laboratory to the patient.* London: Academic Press; 2000.
7. 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.
8. 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. Fracture Intervention Trial Research Group. *Lancet* 1996;48:1535-41.
9. 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: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. *JAMA* 1999;282:1344-52.

10. 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. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. *Osteoporosis International* 2000;11:83-91.
11. 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. Hip Intervention Program Study Group. *New England Journal of Medicine* 2001;344:333-40.
12. Brown JP, Kendler DL, McClung MR, Emkey RD, Adachi JD, Bolognese MA, et al. The efficacy and tolerability of risedronate once a week for the treatment of postmenopausal osteoporosis. *Calcified Tissue International* 2002;71:103-11.
13. 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. Alendronate Once-Weekly Study Group 15. *Aging (Milano)* 2000;12:1-12.
14. Thiebaud D, Burckhardt P, Kriegbaum H, Huss H, Mulder H, Juttmann JR, et al. Three monthly intravenous injections of ibandronate in the treatment of postmenopausal osteoporosis. *American Journal of Medicine* 1997;103:298-307.
15. 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. *New England Journal of Medicine* 2002;346:653-61.
16. Chesnut CH 3rd, Silverman S, Andriano K, Genant H, Gimona A, Harris S, et al. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Groericanup. *American Journal of Medicine* 2000;109:267-76.
17. Ljunghall S, Gardsell P, Johnell O, Larsson K, Lindh E, Obrant K, et al. Synthetic human calcitonin in postmenopausal osteoporosis: a placebo-controlled, double-blind study. *Calcified Tissue International* 1991;49:17-9.
18. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK, et al. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. *JAMA* 1999;282:637-45.
19. Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW, et al. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. *Breast Cancer Research and Treatment* 2001;65:125-34.
20. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K, et al. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. *JAMA* 2002;287:847-57.
21. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002;288:321-33.
22. Beardsworth SA, Kearney CE, Purdie DW. Prevention of postmenopausal bone loss at lumbar spine and upper femur with tibolone: a two-year randomised controlled trial. *British Journal of Obstetrics and Gynaecology* 1999;106:678-83.
23. Berning B, Kuijk CV, Kuiper JW, Bennink HJ, Kicovic PM, Fauser BC. Effects of two doses of tibolone on trabecular and cortical bone loss in early postmenopausal women: a two-year randomized, placebo-controlled study. *Bone* 1996;19:395-9.
24. Roux C, Pelissier C, Fechtenbaum J, Loiseau-Peres S, Benhamou CL. Randomized, double-masked, 2-year comparison of tibolone with 17beta-estradiol and norethindrone acetate in preventing postmenopausal bone loss. *Osteoporosis International* 2002;13:241-8.
25. Cann CE, Roe EB, Sanchez SD, Amaud CD. PTH effects in the femur: envelope- specific responses by 3DQCT in postmenopausal women. *Journal of Bone and Mineral Research* 1999;14:S137.
26. Mosekilde L, Danielsen CC, Sogaard CH, McOsker JE, Wronski TJ. The anabolic effects of parathyroid hormone on cortical bone mass, dimensions and strength — assessed in a sexually mature, ovariectomized rat model. *Bone* 1995;16:223-30.
27. Zanchetta JR, Bogado C, Ferretti JL, Wang O, Sato M, Gaich GA. Effects of LY333334 (Recombinant parathyroid hormone (1-34)) on cortical bone strength indices as assessed by peripheral quantitative computed tomography. Program and abstracts of the 1st Joint Meeting of the International Bone and Mineral Society and the European Calcified Tissue Society; June 5-10, 2001; Madrid, Spain. *Bone* 2001;28 Suppl :S86.
28. Neer RM, Arnaud CD, Zanchetta JR, Prince R, Gaich GA, Reginster JY, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *New England Journal of Medicine* 2001;344:1434-41.
29. Lindsay R, Nieves J, Formica C, Henneman E, Woelfert L, Shen V, et al. Randomised controlled study of effect of parathyroid hormone on vertebral-bone mass and fracture incidence among postmenopausal women on oestrogen with osteoporosis. *Lancet* 1997;350:550-5.
30. Rittmaster RS, Bolognese M, Ettinger MP, Hanley DA, Hodsman AB, Kendler DL, et al. Enhancement of bone mass in osteoporotic women with parathyroid hormone followed by alendronate. *Journal of Clinical Endocrinology and Metabolism* 2000;85:2129-34.
31. Body JJ, Gaich GA, Scheele WH, Kulkarni PM, Miller PD, Peretz A, et al. A randomized double-blind trial to compare the efficacy of teriparatide [recombinant human parathyroid hormone (1-34)] with alendronate in postmenopausal women with osteoporosis. *Journal of Clinical Endocrinology and Metabolism* 2002;87:4528-35.
32. Marie PJ, Hott M, Modrowski D, De Pollak C, Guillemain J, Deloffre P, et al. An uncoupling agent containing strontium prevents bone loss by depressing bone resorption and maintaining bone formation in estrogen-deficient rats. *Journal of Bone and Mineral Research* 1993;8:607-15.
33. Su Y, Bonet J, Deloffre P, Tsouderos Y, Baron R. The strontium salt S12911 inhibits bone resorption in mouse calvaria and isolated rat osteoclast cultures. *Journal of Bone and Mineral Research* 1992;17 Suppl 1:188.
34. Boivin G, Deloffre P, Perrat B, Panczer G, Boudeulle M, Mauras Y, et al. Strontium distribution and interactions with bone mineral in monkey iliac bone after strontium salt (S 12911) administration. *Journal of Bone and Mineral Research* 1996;11:1302-11.
35. Meunier PJ, Slosman DO, Delmas PD, Sebert JL, Brandi ML, Albanese C, et al. Strontium ranelate: dose-dependent effects in established postmenopausal vertebral osteoporosis — a 2-year randomized placebo controlled trial. *Journal of Clinical Endocrinology and Metabolism* 2002;87:2060-6.
36. Bekker PJ, Holloway D, Nakanishi A, Arrighi M, Leese PT, Dunstan CR. The effect of a single dose of osteoprotegerin in postmenopausal women. *Journal of Bone and Mineral Research* 2001;16:348-60.
37. Drake FH, Dodds RA, James IE, Connor JR, Debouck C, Richardson S, et al. Cathepsin K, but not cathepsins B, L, or S, is abundantly expressed in human osteoclasts. *Journal of Biological Chemistry* 1996;271:12511-6.
38. Gelb BD, Shi GP, Chapman HA, Desnick RJ. Pycnodysostosis, a lysosomal disease caused by cathepsin K deficiency. *Science* 1996;273:1236-8.
39. Dimai HP, Müller T, Eder S, Hermann J. Effects of the TNF-alfa antibody imfliximab on serum markers of bone turnover and mineral metabolism in patients with rheumatoid arthritis. *Bone* 2001;28:S179.
40. Deng HW, Stegman MR, Davies KM, Conway T, Recker RR. Genetic determination of variation and covariation of peak bone mass at the hip and spine. *Journal of Clinical Densitometry* 1999;2:251-63.
41. Ensrud KE, Stone K, Cauley JA, White C, Zmuda JM, Nguyen TV, et al. Vitamin D receptor gene polymorphisms and the risk of fractures in older women. For the Study of Osteoporotic Fractures Research Group. *Journal of Bone and Mineral Research* 1999;14:1637-45.
42. Gerdhem P, Brändström H, Stiger F, Obrant K, Melhus H, Ljunggren O , et al. Association of collagen type 1 (COL1A1) Sp 1 polymorphism with femoral neck bone mineral density and wrist fracture in elderly women. *Calcified Tissue International* 2003 (forthcoming).