# OSTEOPOROSIS DIAGNOSIS AND TREATMENT

Márcio Passini Gonçalves de Souza

## ABSTRACT

*Articles that update the state of knowledge regarding osteoporosis run the risk of quickly becoming obsolete because research and studies on osteoporosis today are arousing great interest among researchers, the pharmaceutical and medical equipment industries, governments and even WHO. All orthopedists know about osteoporosis because of its most deleterious effect: osteoporotic fracture. Osteoporosis without fractures does not arouse suspicion because this is a pathological condition with a nonspecific clinical profile. Osteoporotic fractures have an economic cost (from treatment), a social cost (from its sequelae) and a medical cost (from deaths). Many fractures could be avoided through diagnosing osteoporosis prior to the first fracture and thus many temporary and permanent disabilities could be avoided and many lives saved. Awareness of the risk factors for osteoporosis raises suspicions and bone densitometry aids in diagnosis. Treatment should be based on the physiopathology of the disease. Hence, for prevention or treatment of osteoporosis, the activity of osteoclasts should be diminished or the activity of osteoblasts should be increased, or both. Treatment that reduces the incidence of fractures by improving the bone geometry and microarchitecture would be ideal. Newly formed bone tissue needs to have good cell and matrix quality, normal mineralization, a good ratio between mineralized (mechanically resistant) and non-mineralized (flexible) bone, and no accumulated damage. The ideal treatment should have a positive remodeling rate and fast and long-lasting therapeutic effects. Such effects need to be easily detectable. They need to be safe.*

**Keywords** – *Osteoporosis/physiopathology; Osteoporosis/diagnosis; Osteoporosis/prevention & control; Bone fractures.*

## INTRODUCTION

For many years, studies on osteoporosis were relegated to the back burner because this knowledge had little practical value. Today, as well as being a subject greatly researched around the world, knowledge of osteoporosis is objective and useful. Articles that provide updates on this topic rapidly become obsolete because the knowledge on this subject is constantly evolving.

Basic knowledge about osteoporosis has been imprinted in orthopedists' awareness ever since the start of the twentieth century. The word osteoporosis arose from a histological study on an osteoporotic bone by Jean Georges Chretien Frederic Martin Lobstein, a French pathologist, in 1830 *apud* Oliveira[1], but it became popularized among orthopedists as a radiological sign that signified bone rarefaction in fractures caused by low-energy trauma. Radiologists call this same sign osteopenia.

At the end of the twentieth century, the concept of osteoporosis changed progressively from the definition of a very specific disease, made by Albright in 1941, to the current concept of a skeletal disorder encompassing many pathological conditions, in which the microarchitecture of the bone tissue is deteriorating[2,3]. Both the cortical and the spongy bone tissue are affected. The bone microarchitecture may also become modified. The bone mineral density decreases. This leads to impairment of bone resistance to low-energy trauma[4]. Bones become fragile, with a predisposition towards increased occurrence of fractures. The high incidence of these fractures, called osteoporotic fractures, is the factor that gives importance to studies on osteoporosis.

Osteoporosis plays a part not only in increasing the frequency of fractures, but also in increasing the possibilities of different formats, going from fractures with-

Orthopedist in the Osteometabolic Diseases Group, Institute of Orthopedics and Traumatology, HC/FMUSP; President of the Osteometabolic and Degenerative Diseases Committee of SBOT; and President of the Brazilian Association of Bone Metabolism Orthopedics (ABOOM).

Correspondence: Rua Pernambuco 88, 14º andar, 01240-020 São Paulo, SP – E-mail: marciopassini@terra.com.br

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out clinical manifestation, such as so-called morphometric fractures of the vertebral body, and passing through partial fractures to highly unstable comminuted fractures in which anatomical reassembly of the bone is technically impossible. Some fractures may not be detectable; others, such as vertebral body fractures, may leave very painful sequelae; and still others may cause the patient's death or lead to permanent physical disability, such as fractures of the proximal extremity of the femur.

The absolute and relative increases in the size of the elderly population and the unhealthy habits of children and adolescents are leading to very large increases in the incidence of osteoporosis and osteoporotic fractures.

There are many causes for the appearance and/or development of osteoporosis. It is called primary osteoporosis when the causes are natural (menopause and senility). It is called secondary osteoporosis when there is another, primary cause (certain medications, other diseases, sedentarism, etc.). When the causes are unknown, it is called idiopathic osteoporosis.

## DIAGNOSIS

It is said that osteoporosis without current fractures or without microfractures is a silent disease because it does not have specific symptoms that could lead to suspicion of the disease. However, this does not seem to be true. All diseases mediated by osteoclasts are painful. Osteoporosis is perhaps less painful, or perhaps the pain may go unnoticed because it is milder. Many cases of low back pain and other back pain may be of osteoporotic origin, and orthopedists need to be alert to this possibility. Osteoporosis also does not have any pathognomonic clinical signs. Increased thoracic kyphosis and height loss are perhaps the most suspicious signs.

Because of the multifactorial nature of osteoporosis, its syndromic nature and its low clinical manifestations, it is difficult to diagnose. It is mostly diagnosed by orthopedists because of its most deleterious consequence: osteoporotic fracture.

Physicians must therefore remain alert with regard to diagnosing the risk that an individual might have osteoporosis. Attempts to diagnose and treat osteoporosis early on, before the first fracture occurs, have led to studying the risk factors for osteoporosis[5].

### Risk factors for osteoporosis

It is necessary to distinguish between risk factors for osteoporosis and risk factors for osteoporotic fractures. In the former, the possibility that the patient might present osteoporosis is assessed, along with the need to perform subsidiary examinations to prove this. In the latter, the possibility that the patient might suffer fractures because of bone fragility is assessed, and the existence of osteoporosis is thus one of the risk factors.

The risk factors of greatest value for determining whether osteoporosis is present are female gender, white or oriental ethnicity, older age, early inset of the menopause, heredity (presence of osteoporosis or osteoporotic fractures among direct-line ancestors or other relatives), previous history of osteoporotic fractures, nutritional errors (low calcium intake, low vitamin $D_3$ intake or low exposure to sunlight for production of vitamin $D_3$, situations of poor food absorption, etc.), bad habits (excessive intake of coffee, alcohol or tobacco), sedentarism, certain medications (glucocorticoids or anticonvulsants) and diseases such as rheumatoid arthritis and almost all systemic inflammatory diseases.

Although the risk factors for osteoporosis have been well known for a long time, there is still no scientific numerical formula for evaluating these factors separately and within the general context. Moreover, it is possible that there may never be such a formula. Depending on the population studied, these risk factors have different relative values.

The development of densitometers has helped in the diagnosis, but the questions of when to perform densitometry and when to repeat the assessment then arise. Thus, it is again necessary to evaluate the risk factors for osteoporosis.

**Table 1** – Relative values of risk factors for osteoporosis

| Coefficient | Value = 1 | Twice the value | Four times the value | Eight times the value | Absolute value |
|---|---|---|---|---|---|
| Gender | Male | | Female | | |
| Ethnicity | Black | Mixed | White | Oriental | |
| Age | 20 | 50 | 60 | 70 | 80 |
| BMI | > 30 | 27 to 30 | 24 to 27 | 20 to 24 | |
| Age at menopause | > 52 | 48 to 52 | 44 to 48 | Up to 44 | |
| Previous osteoporotic fracture | | | Any osteoporotic fracture | Vertebra | Femur |
| Osteoporotic fracture in parents | | Others | Vertebra | Femur | |
| Habits | Tobacco | Alcohol | Coffee | | |
| Physical activity | Daily | Frequently | Occasionally | Sedentary | |
| Questions on different body systems | | | Anticonvulsants | Rheumatoid arthritis | Corticoid therapy |

Table 1 presents the risk factors for osteoporosis and their value, relative to others, as published in various sources of information. The column "Value = 1" is the basis for the calculations. Thus, individuals with female gender are four times as likely to present osteoporosis, in relation to male gender, and those with Oriental ethnicity are twice as likely to present it, in relation to whites (8/4 = 2), and four times as likely, in relation to blacks (4/1 = 4). Consideration of the various factors may leads to requesting a densitometric evaluation. However, summing the "scores" does not produce any practical result. For example, the presence of any of the factors in the last column on the right side requires a bone densitometry test. Clinical experience, regarding this disease or any other, leads physicians to suspect that the disease may be present and look for a diagnosis. In the case of osteoporosis, the suspicion arises from the existence of risk factors.

## Densitometry

Densitometers are devices that generate a double band of X-rays that crosses a region of the patient's body. The radiation emitted is gathered in a collimator and the quantity of calcium is evaluated according to the area measured. The results obtained are analyzed in a computer and compared with a database of individuals of the same ethnicity, weight, height and age (20 to 100 years). The results are presented in grams/cm$^2$ and compared with the mean for individuals aged 20 years (T score), which represents the peak value for bone mass. The mean bone mineral density values are also compared between individuals of the same age (Z scores). The relative percentages and standard deviations (SDs) of the means are calculated. In accordance with the WHO consensus, the results are considered to be normal when the densitometry shows down to –1 SD in the T score; osteopenia, from –1 to –2.5 SDs and osteoporosis, from –2.5 SDs downwards. Osteoporosis is also deemed to be present when, in addition to SD < –2.5, the patient presents an osteoporotic fracture. Today, any patient with an osteoporotic fracture is considered to present osteoporosis. Z scores less than or equal to –2 are suggestive of possible secondary osteoporosis.

Like any subsidiary examination, densitometry should be performed when there are sufficient indications of the possibility that the patient has the disease. Suspicion is aroused through the existence of risk factors for osteoporosis. In the absence of risk factors, the rule is to firstly make densitometric evaluations on all individuals over the age of 65 years and on all women aged 50 years and over who reached the menopause at an early age. The examination should be repeated every one to three years, depending on clinical criteria, or for checking on treatment.

## Risk factors for osteoporotic fractures

The risk factors for osteoporotic fractures are the same risk factors as for osteoporosis, with the addition of the densitometry results. Risk factors for falls are also important, but it must be borne in mind that ordinary low-energy trauma does not cause fractures in healthy individuals. The concept of osteoporotic fracture is that this is "a simple or complex fracture that occurs in individuals with apparent or non-apparent osteoporosis, caused by high-energy trauma".

There is no confirmed relationship between occurrences of fractures and the densitometry result. Densitometry measures the calcified bone mass, but it does not measure the quality of this bone mass. One well-known case is the increased bone mineral density seen from densitometry that results from use of sodium fluoride, which was greatly used in the past for treating radiological osteoporosis, but was found to promote greater bone fragility. Another example is given by strontium, in the form of strontium ranelate, which is a promising means for treating osteoporosis. Because of its greater atomic mass and atomic radius, it produces higher bone mineral density readings from densitometry through greater attenuation of the X-ray beam from the densitometer.

Patients who are classified as presenting "densitometric osteoporosis" certainly have higher incidence of fractures than do other individuals, and this rate is inversely proportional to bone mineral density. However, the number of osteoporotic fractures is much greater among individuals who are classified as having "densitometric osteopenia". Even "densitometric normal" individuals suffer osteoporotic fractures in large numbers. This occurs because the "normal" and "osteopenic" populations are larger than the osteoporotic population[6].

One serious public health problem is therefore how to identify individuals who do not present densitometric osteoporosis but are susceptible to osteoporotic fracturing. Currently, an epidemiological index named the FRAX (Fracture Assessment Tool) index is being studied under sponsorship from WHO[7]. This makes statistical evaluations on risk factors presented by individuals and provides the percentage likelihood that these individuals might suffer an osteoporotic fracture over the

next ten years[8]. In Brazil, there are already studies in progress aimed at establishing the FRAX index for the Brazilian population.

In placebo-controlled clinical studies on patients treated with oral bisphosphonates, losses of densitometric bone mass in the placebo group are accompanied by increased incidence of fractures, while gains in densitometric bone mass of up to 5% are accompanied by proportional diminution of this incidence. Above 5%, the diminution of the prevalence of fractures continues, but does not maintain proportionality with the gains in densitometric bone mass[9].

## TREATMENT

Once a diagnosis of osteoporosis has been established and the risk of osteoporotic fractures has also been established, it needs to be decided whether the treatment should prophylactic and/or curative. Many interventions serve both purposes. It is obvious that when osteoporosis is prevented or treated, prevention of osteoporotic fractures is also provided.

Before discussing treatments, a brief review of BONE REMODELING is useful.

Bone is a type of living tissue that constantly undergoes an exchange process from old to new tissue. The mediators in this process are osteocytes. From time to time (around every thousand days), osteocytes undergo apoptosis, i.e. programmed cell death. Close to the time of apoptosis, they produce signals for pluripotent mesenchymal cells to form osteoblasts.

A similar stimulus occurs when the bone is subjected to physical effort for which it is unprepared. Either through pressure on the cell membrane proteins[10], or through stimulation of primary cilia (the organelles of osteocytes that detect these tensions), signals are sent to the mesenchymal cells, to trigger osteoblast formation.

Osteoblasts produce the RANK (Receptor Activator of Nuclear factor Kappa beta) factor, which signals to hematopoietic cells for them to form osteoclasts, and also activates the brush border of these osteoclasts.

Over a 20-day period, the osteoclasts reabsorb some of the bone tissue, thus forming Howship's lacunae. Osteoblasts then fill these lacunae with protein matrix and lastly, deposit hydroxyapatite crystals in them. This process takes 180 days to complete.

If this remodeling process is disturbed, through greater proportional action of osteoclasts in relation to osteoblasts, the bone tissue formation will be impoverished. Depending on the severity of the situation, this may give rise to osteopenia or to osteoporosis.

Thus, in preventing or treating osteoporosis, osteoclast activity needs to be decreased or osteoblast activity needs to be increased, or both of these.

The ideal would seem to be to stimulate bone formation by stimulating the action of osteocytes or osteoblasts. However, while stimulation of osteoclasts produces action within 20 days, the osteoblasts will take 180 days to repair the lacunae left by the osteoclasts. This explains why certain anabolic treatments, i.e. treatments that stimulate osteoblasts, do not always achieve the expected results.

The following are anabolic treatments: physical activity, calcitriol (vitamin D), associations between calcium and calcitriol, anabolic steroids, growth hormones, parathormone (PTH) and its derivative teriparatide, and strontium ranelate.

The following are anticatabolic treatments, i.e. treatments that inhibit the action of osteoclasts: physical activity, associations between calcium and calcitriol, active metabolites of calcitriol, estrogen replacement therapy, hormone replacement therapy (HRT), SERMs (selective estrogen receptor modulators), bisphosphonates, osteoprotegerin (OPG) and strontium ranelate.

### Physical activity

This is the cheapest means of prevention and coadjuvant for treatments. Exercises with weights and speed exercises are the most effective ways of gaining bone mass. In addition, the gain in muscle mass and improvement in the speed of the neuromuscular motor response diminish the numbers of falls and the risk of fractures among patients. The piezoelectric effect of physical activity, or the action of the primary cilia, stimulates the osteocytes (via osteoblasts) to promote the formation of new bone.

Comparison between elderly people who practice physical activity and sedentary elderly people shows that the incidence of hip fractures among active individuals is lower[11].

### Calcium supplementation

Calcium forms part of the hydroxyapatite crystal ($Ca_{10}(PO_4)_6(OH)_2$), which gives mechanical resistance to bone tissue. In the composition of bone tissue, this crystal corresponds to 65%. Calcium also plays a part in blood coagulation, metabolic regulation through

metalloenzymes (alpha-amylase, phospholipases, etc), hormone and neurotransmitter secretion and cell adhesion. Because of the presence of calcium in the troponin molecule, which regulates the contractility of actin and myosin, it participates in muscle contraction, including in the heart. The importance of this action means that, biologically, calcemia levels need to remain as constant as possible.

In nature, calcium is present in all living organisms. The greatest sources are milk and dairy products. Sardines, beans and vegetables with dark leaves are also very rich in calcium. However, it is not always the case that consumption of foods rich in calcium results in absorption of calcium in the intestine. This absorption depends on whether the calcium is in the form of absorbable salts. Thus, the presence of oxalic acid, vitamin C, phytates (present in cooked greens), certain fibers, proteins and even lactose may cause the formation of insoluble or non-absorbable compounds.

Another source of calcium is the exoskeleton of mollusks. From this, calcium carbonate is extracted, which is soluble and absorbable in acid pH. Because of this chemical characteristic, calcium carbonate is poorly absorbed in elderly people (because of hypochlorhydria) and in patients who take antacids, etc. In these situations and in cases of nephrolithiasis, calcium citrate is used because it is more absorbable and acidifies urine. Calcium orthophosphate is used in cases of elderly people with low phosphorus intake (rare) who are institutionalized and have difficulties in feeding themselves.

In the intestine, calcium is absorbed via paracellular and transcellular pathways. The paracellular pathway is passive and depends on the quantity of calcium in the food bolus, the speed of digestion and the pH of the chyle and calcium salt, along with the presence of other products already cited above. The transcellular pathway is active and depends on the presence of calbindin, which is synthesized by vitamin D.

All the calcium present in the blood is filtered by the renal glomeruli and most of it is reabsorbed by the tubules. Some of it is eliminated (100 to 300 mg per day) through the urine and needs to be replaced.

Among individuals over the age of 50 years, with or without HRT, it is essential to supplement the diet every day with up to 1500 mg of calcium, taken as two doses. A non-dairy daily diet has up to 700 mg and a diet rich in dairy products has up to 950 mg. Additional calcium is provided so that the organism can make use of what it requires.

The pharmaceutical products are named in accordance with the quantity of elemental calcium that the tablets or sachets contain and not the quantity of the salt. Thus, 1250 mg of calcium carbonate appears as "calcium 500".

Administration of calcium alone is efficient for diminishing the incidence of fractures[11].

## Vitamin D

Vitamin D is a "quasi hormone". It acts on the intestinal absorption of dietary calcium and on reabsorption of urinary calcium in the renal tubules. It reduces the levels of PTH and stimulates osteogenesis by the osteoblasts. It has antibiotic action on the respiratory tree. It acts to modulate the equilibrium of the CNS. It facilitates increases in muscle strength, particularly in cases of sarcopenia. It stimulates cell differentiation and inhibits cell proliferation, thus acting as a protector against breast, prostate and intestinal cancer. The need for vitamin D increases with age[12]. It is produced naturally through the action of UVB rays in sunlight on the 7-dihydrocholesterol circulating under the irradiated skin, thereby transforming it into cholecalciferol. This molecule, which already contains one hydroxyl group, receives another one on its carbon 25 when it passes through the liver, thus forming calcidiol or 25-hydroxycholecalciferol. A third hydroxyl is attached to its carbon 1 in the kidneys, thus forming calcitriol or 1,25-dihydroxycholecalciferol. Cholecalciferol or vitamin D3 exists in the liver of cold-water fish, in eggs and in enriched milk. There is little in human milk. Its isomer ergosterol, or vitamin D2, exists in plants. Vitamins D3 and D2 and calcidiol are inactive. Calcidiol is the depot form. Calcitriol and its metabolite alfacalcidol are the active forms regarding absorption of calcium from the intestinal lumen and reabsorption of urinary calcium in the renal tubules. They have a very short life and, for this reason, they are not assayed. Calcidiol can be assayed and should be maintained between 32 and 100 ng/ml of serum[13]. It is requested from laboratories as serum "25-OH-vitamin D". To maintain this level, the ideal intake is 800 to 1200 IU of vitamin D3 per day.

Several formulations are available on the market. When associated with calcium, the concentration is generally 200 IU/tablet. Other preparations exist, consisting of associations of cholecalciferol with retinyl palmitate (vitamin A) and with alpha-tocopherol (vitamin E). For example, Ad-til contains 250 IU of vitamin D

and 1250 IU of vitamin A per drop (40 drops/ml). Forty drops per day is used to restore the ideal concentration in the serum (for around three months), and 40 drops per week to maintain it.

The association of calcium and D is efficient for diminishing the incidence of fractures[14].

## Anabolic steroids and growth hormones

These act to improve the formation of protein matrix and stimulate osteoblasts. Because of their adverse effects, they are little used. In cases of secondary osteoporosis due to male hypogonadism, urologists frequently use methyl testosterone with efficient results.

## Teriparatide and PTH

Parathormone is formed by 84 amino acids arranged in a linear chain. Teriparatide is its homologue, with amino acids 1 to 34 only, obtained by means of the recombinant DNA technique. Together, when administered continuously, they increase the binding of RANK to preosteoclasts, thereby stimulating replication of the latter, and to osteoclasts, thereby stimulating their bone tissue reabsorption action. Thus, PTH and teriparatide have great capacity for bone reabsorption (cystic fibrous osteitis). However, when used daily in small doses, they inhibit the RANK system and increase OPG levels, thus inhibiting bone reabsorption. In this case, they also stimulate the replication and activity of endosteal and periosteal osteoblasts. Through this, they increase the thickness of the cortical bone, the cross-sectional area of the bone and the thickness and connection of the trabeculae[15]. This gives greater mechanical resistance to the bone[16]. They are used in the form of daily subcutaneous microinjections, by means of a "pen" with 28 doses. This treatment is often indicated for patients who are at high risk of fractures and/or refracturing[17]. Currently, many studies seeking to associate teriparatide use concomitantly or sequentially with anti-reabsorptive agents are being developed[18-20].

## Hormone replacement therapy (HRT) and estrogen replacement therapy

These are efficient for preventing postmenopausal osteoporosis, but not for treating it. They should be started soon after the menopause, under supervision by a gynecologist because of their potential adverse effects. The greatest problem is the increase in occurrences of breast cancer, along with thromboembolic disorders.

## SERMs

SERMs or selective estrogen receptor modulators are used when patients are at an increased risk of breast cancer. They inhibit estrogen receptors in the breasts and uterus, thus protecting these two organs against the deleterious action of estrogen. The type of SERM most used is tamoxifen.

Other SERMs have been developed as substitutes for HRT, for preventing and treatment of osteoporosis, with estrogen-stimulating action on the estrogen receptors of bones, the cardiovascular system and lipids. Thus, they prevent and treat osteoporosis, prevent hypercholesterolemia and vascular atheromatous plaque, and do not stimulate the development of breast and uterine cancer. Raloxifen hydrochloride and lasofoxifene are examples.

## Bisphosphonates

Bisphosphonates (or geminal bisphosphonates) are polyphosphates that have at least one P-C-P connection (phosphorus – carbon – phosphorus) in the molecule. They were first synthesized by Menschutkin in 1865, for use as industrial anticorrosive agents. Subsequently, they started to be used as softeners for "hard water" (alkaline water) in laundries, and in water pipes (to impede the deposition of calcium carbonate).

In 1968, Fleish and Russel discovered pyrophosphate in plasma and urine and, in 1970, they discovered that it inhibited precipitation of calcium carbonate in the urinary vessels and passages, thus constituting a biological "softener". Because etidronate had been in clinical use for treating bone metabolism diseases since 1968, they started to investigate the use of bisphosphonates to treat osteoporosis and Paget's bone disease.

The bisphosphonate molecule is formed by a central carbon atom to which two phosphate radicals, one $R_1$ radical (ideally a hydroxyl group) and one $R_2$ radical (ideally containing a cyclic chain and a nitrogen atom) are bonded. Depending on the spatial formation of this molecule, it will have greater or lesser capacity for adsorption on hydroxyapatite molecules. It is known that the P-C-P chain with a hydroxyl group on each of these atoms is the best formation for adsorption on hydroxyapatite.

This adsorption is important because when osteoclasts reabsorb bone tissue, they also absorb bisphosphonates. Inside the cytoplasm of phagocytes, aminated bisphosphonates (i.e. with nitrogen in the $R_2$ radical)

act on mevalonate to inhibit an enzyme called farnesyl pyrophosphate synthase (FPPS). This enzyme promotes the transformation of geranyl pyrophosphate into geranyl-geranyl pyrophosphate and farnesyl pyrophosphate. These metabolites promote prenylation of the small proteins that are essential for the brush border to function and for osteoclasts to survive. Thus, by breaking the mevalonate chain, the bone absorptive function of osteoclasts is inhibited.

The bisphosphonates that can be used in osteoporosis therapy are differentiated according to their capacity for adsorption of hydroxyapatite crystals and their power to inhibit osteoclast function.

The following bisphosphonates have been registered in Brazil for treating osteoporosis: sodium alendronate, sodium pamidronate, sodium risedronate, sodium ibandronate and zoledronic acid. Comparison of antiresorptive power in relation to etidronate (taken to have a value of one) shows that alendronate is 1,000 times more powerful, risedronate 5,000 times and zoledronic acid 10,000 times. Regarding the adsorptive capacity, the adsorption affinity constant for etidronate is 1.2; risedronate, 2.2; ibandronate, 2.3; ibandronate, 2.9; and zoledronic acid, 3.4[21].

Bisphosphonates for oral use have low solubility and, for this reason, should be administered while fasting, with a glass of pure water (mineral water is not recommended). Patients should continue to fast for another half hour. Since these substances are aggressive to the esophageal mucosa, patients should lie down during this first half hour, while the stomach is still emptying, so that esophageal reflux is avoided.

Only 1% is absorbed (0.6% for ibandronate). Of this, 51% is eliminated via the kidneys, without metabolization, while 49% is adsorbed in the hydroxyapatite, particularly in new bone material. When bisphosphonates are released into the bloodstream through the death of osteoclasts or through "de-adsorption", they are again adsorbed into hydroxyapatite. Some types, such as risedronate, have greater "de-adsorption", which explains their better distribution throughout the bone tissue and their multi-site effect.

It is likely that these known differences, and others that remain unknown, cause the differences in the antifracture actions of different bisphosphonates. Whereas they are similar in the way they act, they differ in their power of action. Thus, they act differently in relation to remission of densitometric osteoporosis and diminution of the prevalence of fractures.

It seems that the best quality of alendronate is the clinical experience of its use that has been accumulated. Since this was the first effective drug against osteoporosis, it has been in use for the longest time and by the greatest number of individuals. Its greatest problem is that many similar drugs exist: these have not been tested clinically but are frequently prescribed as substitutes for the original salt. Another problem is the current suspicion that fractures can be caused through strong inhibition of bone modeling (frozen bone), when this drug is used for a long time. Alendronate has been tested at a dose de 10 mg per day, orally. A bridge study has shown that a dose of 70 mg per week is also efficient for inhibiting the incidence of osteoporotic fractures. A presentation consisting of 70 mg and 2,800 IU of vitamin $D_3$ for weekly use was recently launched, and one with 5,600 IU, also for weekly use, is to be launched.

Risedronate is the drug that has been used for the second longest time, with the second largest population of users. Its best quality is its proven rapidity of action and its multi-site efficacy of anti-fracture action, particularly with regard to hip fractures, as demonstrated in a specific clinical study, the Hip study[22]. It was originally tested and launched at a dose of 5 mg per day for oral use. A bridge study demonstrated that it was effective at a weekly does of 35 mg, and a new bridge study has now demonstrated that monthly use at a dose of 150 mg is valid[23].

The best quality of ibandronate is its formulation of 150 mg, for oral use once a month. It has now been shown that oral bisphosphonates can be administered in larger doses at longer intervals, while maintaining their effect as seen through densitometric evaluations. Originally, it was launched as doses of 2.5 mg for oral use, daily.

Zoledronic acid differs from the other drugs mentioned above because it is for intravenous use, as an annual dose. This drug too has been studied specifically for patients with hip fractures, in the Horizon RFT study[24], which showed that there was lower incidence of recurrent fractures in the active drug group, and that the treated group had longer survival than the placebo group. For this reason, and because of the advantage that it can be used for bedridden patients, it is often indicated for use among patients who have recently undergone operations to treat fractures of the proximal femur. It also has the advantage of adherence to treatment, because of the annual dosage. Currently, it is registered only for treatment, but the manufacturer is awaiting authorization for its additional use, for prevention of osteoporosis.

The percentage diminution of fracture incidence and the percentage remission of densitometric conditions achieved by different bisphosphonates and other therapies cannot be compared because the populations studied in different investigations were very different from each other. There are still not enough comparative head-to-head (drug versus drug) studies to establish any great differences between the treatments[25].

## Osteoprotegerin

Osteoprotegerin is a product that is coming onto the market now, after several years of research. It acts by inhibiting RANK, thereby impeding it from binding to osteoclasts and thus stimulating the latter to reproduce and activate its brush border.

## Strontium ranelate

Strontium ranelate is a product for treating osteoporosis that presents two actions: it is anti-reabsorptive and, at the same time, it is pro-formative[26].

It is a salt of ranelic acid with two strontium atoms in each molecule. It is absorbed in the intestine, and vitamin D does not have any effect on this absorption. Ranelic acid is not metabolized, has little bonding to plasma proteins, does not accumulate in the human organism and is rapidly eliminated through the kidneys, thereby leaving the two strontium atoms free to be adsorbed into hydroxyapatite (small quantities replace the calcium atoms in the composition of the crystal)[27].

The bioavailability of strontium, administered as 2.632 g of hydrated strontium ranelate (2 g of the anhydrous form), is 27%[28]. The maximum serum concentration of strontium is reached in three to five hours. The half-life is 62 hours and the proportion that is not adsorbed into the hydroxyapatite is excreted through the kidneys (57%) and intestine. Strontium does not bind to plasma proteins, it is not metabolized and it does not inhibit the P450 cytochrome system. It reaches an equilibrium point after two weeks, and the half-life is 10 weeks.

Strontium is a chemical element that is very similar to calcium and magnesium. Its valence is +2 (like calcium and magnesium); it has 38 electrons distributed in four layers (calcium has 20 in three layers); its atomic radius is 215 (for calcium, it is 197); and its ionic radius is 116 (for calcium, it is 100). These similarities cause the organism to confound them, in relation both to intestinal absorption and to participation in hydroxyapatite crystals. The absorption depends on the salt (ranelic acid was developed for this reason), the dose (in this case, 2 g), the presence of calcium in the diet (administered in the evening, three hours after dinner), renal function and the animal species that is studied.

Since strontium diminishes the activity of vitamin D3 hydroxylase, its excess may lead the bone to osteomalacia. At the recommended small doses, it stimulates normal calcification of the osteoid tissue.

In bone tissue cultures, it stimulates replication of pre-osteoblasts, thereby increasing the numbers of osteoblasts and thus increasing bone formation. It also stimulates the formation collagen.

On the other hand, it reduces the differentiation of osteoclasts and reduces their activity. For this reason, it inhibits bone reabsorption. It is therefore pro-formative and anti-reabsorptive.

There are increases in the bone formation markers (alkaline phosphatase and pro-peptide C), while there are decreases in the bone reabsorption markers (serum C-telopeptide and urinary N-telopeptide), as early as the third month, thus confirming its double action.

In animal tissue and human biopsies, it has been shown that it improves the bone microarchitecture[29,30]. It acts by stimulating the trabecular volume, thereby increasing the number of trabeculae and their thickness. It does not impair bone quality and mineralization, and thus it does not leave mineral defects.

In addition to formation of endosteal bone, it stimulates the production of periosteal bone, which improves the macroarchitecture and resistance of the bone[30].

More recent studies using state-of-the-art technology such as high-resolution peripheral quantitative computed tomography (HR-pQCT) have suggested that strontium ranelate acts more rapidly and more effectively towards formation of new cortical and trabecular bone than does alendronate[31]. This would suggest that it is more effective in preventing fractures.

The presence of strontium in the bone increases the absorption of X-rays, as seen in densitometry. A recently published comparative study stated that, for strontium ranelate, bone mineral density measurements report at least 75% efficacy against fractures, while for bisphosphonates, this estimate is between 4% and 28%[32].

The Soti and Tropos studies,[33,34] over a period of up to five years, proved the efficacy of strontium ranelate in patients with osteoporosis, from the initial stages to more advanced stages, including among populations of patients aged 80 years and over. These studies proved that the risk of vertebral fractures was reduced by 45% and the risk of hip fractures was reduced by 43%, both

in patients without previous fractures (45%) and in patients with fractures (41%).

### Choice of treatment

The ideal treatment would be one that diminished the incidence of fractures through improving the bone geometry and its microarchitecture. The recently formed bone tissue should be of good cell and matrix quality and present normal mineralization with good proportions between mineralized bone (mechanically resistant) and unmineralized bone (flexible), without accumulation of damage. The ideal treatment should have a positive remodeling rate and a rapid and long-lasting therapeutic effect. This effect should be easily detectable. The treatment should be safe.

However, this ideal treatment still does not exist. The various treatments cited above each present some of these ideal characteristics and do not present others. The choice of treatment for each patient depends on the patient's characteristics, the severity of the pathological condition and the physician's knowledge of the therapeutic arsenal as a whole and of the medication that will be prescribed in particular.

The problem of the cost of the treatment will always be present, especially with regard to avoiding abandonment of the treatment. Physicians (and society) have the duty to pressure the public authorities to allow the use of the best treatments that their conscience and knowledge indicate.

It is preferable to use a medication for which the physician has good knowledge of the indications, adverse effects, interactions with other drugs and contraindications in relation to other pathological conditions presented by the patient.

Organic molecules present spatial isomers that are chemically equal but may not be biologically equal. Cheaper similar and generic drugs may even be more effective than the branded products, but may not have been tested in accordance with the rigorous requirements of the registration agencies. In relation to a long-term disease that affects elderly patients, there is no time to waste on experiments with cheaper products.

Some indications are formal: the use of teriparatide for patients at high risk of osteoporotic fracture; the use of risedronate when fast multisite action is required, especially in order to prevent hip fractures; the use of zoledronic acid when adherence to treatment for at least one year is required; the use of bisphosphonates when the patient is bedridden; the use of zoledronic acid for bedridden patients following operations to treat hip fractures; and the use of teriparatide and strontium ranelate when reactivation of bone metabolism that seems to be "frozen" through prolonged use of alendronate is required.

It is obvious that in cases of secondary osteoporosis, it is important to treat the primary cause. Nonetheless, in all cases of osteoporosis, whether primary or secondary, patients may benefit from any of the above treatments.

## FINAL REMARKS

### Assessment of treatment efficacy

The ideal assessment would consist of mechanical resistance tests in association with anatomopathological or histomorphometric examinations on the treated bones. Decreased incidence of vertebral and non-vertebral osteoporotic fractures, including at the proximal extremity of the femur, would also be good ways of evaluating this. The problem is the practicality of these evaluations. Thus, the fallback method is to assess the reduction of the relative risk (RR) of occurrence of an osteoporotic fracture, which has been established by statisticians based on clinical and laboratory studies.

There is controversy regarding the extent to which each drug reduces the relative risk of each fracture in each population in particular. However, there is no controversy regarding orthopedists' moral (and legal) obligation to treat patients with osteoporotic fractures or to refer them for treatment.

The best evaluation method continues to be densitometry. Results over periods of less than one year are inconclusive and, for this reason, the first evaluation should be made after one year of treatment, except in cases of osteoporosis induced by glucocorticoids (which should be done every six months). When the annual densitometry evaluation shows a gain in bone mass greater than 2%, evaluations can then be undertaken every two years.

Vertebral quantitative computed microtomography provides images of the trabecular bone, from which the efficacy of the treatment can be inferred. This is not used in daily clinical practice because it is performed in a piece of equipment that is still very expensive. However, it is increasingly used in research.

Biochemical markers for bone turnover are of great interest for clinical research or, in cases of doubt regarding treatment efficacy, for very short-term clinical evaluations. Serum markers for bone formation and markers for bone reabsorption (which are generally urinary) may

provide information after only three months of treatment. The bone formation markers most commonly evaluated are total serum alkaline phosphatase and its bone fraction, osteocalcin and serum type I carboxyl and amino-terminal pro-collagen peptides (serum C and N pro-peptides). The bone reabsorption markers most commonly evaluated are urinary hydroxyproline, serum and urinary N (NTx) and C (CTx) telopeptides, urinary pyridinoline and deoxypyrinoline (DPD), serum tartrate-resistant acid phosphatase and calciuria.

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