Medical management following an osteoporotic fracture

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Summary Osteoporotic fractures are common and account for an important medical impact and high induced health-related costs. The most common fracture sites are the vertebra, wrist, proximal humerus and proximal femur. Osteoporosis must benefit from a medical treatment after a fragility fracture. This management is currently insufficient in France, although diagnostic tools (DEXA scan), effective treatments and guidelines are available and have been widely disseminated. Orthopaedic and trauma surgeons must emphasize to patients with a fracture that they need to consult their general practitioner or rheumatologist to decide how their osteoporosis will be diagnosed and treated.

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Introduction

Osteoporosis is the most common brittle bone disease. It is defined as "a bone disease characterized by a reduction in the mechanical strength of bone leading to increased fracture risk" [1]. Fragility fractures, which occur spontaneously or after a low-energy trauma, are a complication of progressive loss in bone mass and changes in bone micro-architecture. The most common fracture sites are the vertebra, wrist and proximal femur.

Because of high prevalence, significant morbidity, additional mortality and socioeconomic consequences, osteoporosis is a public health concern for all physicians, especially for surgeons who are treating a patient at the time of fracture. Yet, osteoporosis is too often a disease that is trivialized and lumped into the aging phenomenon, which leads to insufficient diagnosis and treatment.

Osteoporosis and fragility fractures

It is estimated that one out of every two women will have a fracture between menopause and the end of her life. After 80 years of age, 70% of women have osteoporosis and 60% have had one or more fractures. Osteoporotic fractures are less common in men (about 15% of men above 50 years of age have had fractures) but they can be more serious [2].

Except for the skull, cervical spine, first three thoracic vertebrae, hands and toes, a fragility fracture can occur at all bone sites. A low-energy trauma is defined as a fall...
from standing height or a maximum of 50 cm, either during walking or after having come to a stop. Osteoporosis can also increase the likelihood of a fracture during a high-energy trauma. Bone cracks (incomplete fractures without cortical breach) can also be fragility fractures, although some of them are associated with excessive mechanical loading that leads to bone failure (fatigue or stress fractures). Recent data suggests that fractures occurring in adolescents or young adult result in a greater risk of osteoporosis after the age of 50 [3,4].

Fractures of the proximal femur are the most serious; the yearly incidence in France is estimated at about 70,000. These fractures are associated with significant morbidity and mortality, with elderly subjects often losing their autonomy and having a two to four times greater risk of dying within a year than the general population. This increased mortality rate with all types of fractures is particularly evident in men and women above 75 years of age [5]. The incidence of vertebral fractures is difficult to evaluate because they are often mildly- or non-symptomatic (estimated at 150,000 per year in France). We are often unaware of these fractures (only 1/3 are diagnosed), which puts emphasis on the importance of clinical (height, kyphosis of thoracic spine) and radiological screening when a menopausal woman presents with atypical and persistent back pain. The incidence increases with age: 5.5 per 1000 people/year in women 55–59 years of age to 29.3 in women 75–79 years of age. The risk of recurrence is high. Women who have had a vertebral fracture have twice the risk of another one within a year [6]. This risk, also seen with non-vertebral fractures, is greatest in the two years following the first fracture in menopausal women [7]. There are about 35,000 distal radius fractures per year. They result in a significant transient functional disability and can be complicated by complex regional pain syndrome. As with all vertebral fractures, these “sentinel fractures” are a warning of other fragility fractures and should trigger a search for an underlying osteoporotic disease. This approach could avoid the subsequent occurrence of more serious fractures.

After 65 years of age, one in three women will fall and 5% of these falls will lead to a fracture, with 1% being proximal femoral fractures. Preventing falls should be a priority to reduce fracture incidence. Known risk factors for falls should be evaluated during the initial clinical examination: visual problems, neuromuscular and orthopedic problems, intake of psychotropic medicines or medicines that induce orthostatic hypotension, obstacles in the patient’s home. Recommendations for the prevention of falls in elderly patients with a management algorithm were developed by the American Geriatrics Society in 2001 [8].

**Insufficient management**

After a fracture, the osteoporosis management rate (diagnosis and treatment) is very low in all countries. A study performed with British general practitioners found that only the occurrence of a vertebral fracture increased the prescription (rate) of anti-osteoporosis drugs in the year following the fracture [9]. In France, the guidelines, which non-specialists find to be very complex, will be updated soon. A study performed in 2007 with 2658 French general practitioners (APOTEOS) found that these physicians took the risk factors outlined in the French AFSSAPS guidance into consideration when determining the appropriate treatment [10].

Cuddihy and co-workers monitored women above 45 years of age who had a distal radius fracture for an average of three years (range of 1 to 6.7 years). This study found that only 18% were treated for osteoporosis, although 83% had consulted with a physician in the year after the fracture (other than the orthopaedic consultation) [11]. Similarly, diagnostic evaluations in this population are quite rare: only 5% of patients had a DEXA scan performed within one year of the fracture. Another retrospective study found that treatment (HRT, calcitonin, bisphosphonates) was prescribed in 44% of cases after vertebral fracture and in only 21% and 23% of cases after proximal femur and distal radius fractures, respectively [12]. Three of four patients were not being treated before the fracture and 14% received treatment after. This lack of management, most evident in osteoporotic women with fractures, also exists in the male osteoporotic population. A study found that only 7% of men with an osteoporotic fracture are being treated for osteoporosis [13].

However, there are signs of progress in more recent publications. Gardner and co-workers evaluated an active protocol that aimed at improving management after proximal femur fracture in 80 patients hospitalized in the orthopaedic unit [14]. Patients who were educated about osteoporosis during their hospital stay were given a DEXA scan and treated more often than patients who were discharged only with a brochure on fall prevention (42% versus 19% in the second group).

Three very recent publications found that management was improved after distal radius fracture. If a DEXA scan was prescribed while a female patient was still in the orthopaedic unit for a distal radius fracture, the likelihood of therapeutic management increased 2.5 times [15]. When the intervention was made later on, within 6 months of the distal radius fracture, and targeted general practitioners, twice as many DEXA scan were prescribed (53.3% vs. 26%) and therapeutic management increased three-fold (28% vs. 10%) [16]. A Canadian study with a similar approach confirms this data and suggests that the persistence of treatments being prescribed to these female patients was very good (more than 80% after one year) and that the strategy has a positive impact on health economics: reduction in costs, improvement in quality of life [17].

These data should encourage orthopaedic and trauma surgeons to direct fragility fracture patients to their general practitioner or another facility to manage the osteoporosis. Access to these “fracture channels” depends on surgeon motivation and could be facilitated by automated processes (education by nurses, mailing, etc.).

**Diagnostic and prognostic approach**

Evaluating fracture risk is pivotal to the treatment decision. It is based on the evaluation of clinical risk factors and measurement of bone mineral density (BMD).
Diagnostic investigation is absolutely necessary

But before this step, it is essential to look for a local cause for the bone brittleness (tumour or osteolytic dysplasia) or for a systemic reason for the fragile bone disease (Table 1). The priority is to rule out a tumour (especially myeloma), then osteomalacia, before looking for other reasons for the bone fragility. The first series of tests (calcemia, phosphatemia, creatininemia, alkaline phosphatase, calcuria over 24 hours and 25-OH vitamin D) must be normal in cases of post-menopausal or idiopathic osteoporosis. This minimum screen however is not officially recommended. Conversely, any abnormal finding in this screen will direct the second round of tests (PTH, TSH, testosterone, LH and FSH or prolactin, cortisol, iron saturation coefficient and ferritin, etc.).

Spinal X-rays should be performed if the patient presents with pain or is 4 cm shorter in height than when he/she was a young adult [18]. These are used to look for vertebral fractures and signs of malignancy. With the slightest suspicious sign (cortical lysis, dissolving pedicle sign, significant retreat of the posterior wall or asymmetric fracture), secondary examinations (MRI, CT scan or bone scan) will help to decide on and guide a bone biopsy for a pathology diagnosis.

Fracture risk evaluation to decide on treatment

The decision to start an anti-osteoporosis treatment is based on an evaluation of fracture risk through a careful analysis of clinical features (risk factors) and BMD measurement. The risk of recurrence must be evaluated with a current fracture, knowing that the risk is higher than without a fracture. This situation often requires that an osteoporosis treatment be prescribed for secondary prevention.

Clinical evaluation

A certain number of clinical risk factors, both intrinsic and extrinsic to the patient, must be considered when determining the individual risk of a vertebral or peripheral fracture. Typical clinical factors to evaluate are age, gender, personal and family history of osteoporotic fracture, history of extended cortisone treatment, low body mass index and smoking. A list of the main risk factors has been established by the French AFSSAPS (Table 2). Other than corticosteroids, the intake of aromatase inhibitors and GnRH analogues must be investigated, as these treatments can accelerate bone loss and increase fracture risk.

DEXA scan to measure BMD

A dual-energy x-ray absorptiometry (DEXA) scan is the gold standard method to evaluate bone mass. Measurements at the lumbar spine (L1 to L4) and proximal femur have been chosen as they are the most reproducible and narrowly correlated to the fracture risk [19]. This is a simple, reliable, reproducible, non-invasive, inexpensive examination that is reimbursed in France for the indications approved by the French HAS (Table 3). One of the validated indications in men and women is a history of fracture, as long as the fracture was non-traumatic. The measurement of bone mineral density (in g/cm²) is used to quantify bone loss and define bone status relative to thresholds defined by the World Health Organization (WHO) (Table 4). A patient’s BMD is compared to the normal curve of the same gender and race in the general population and used to define the Z-score (comparison to the average value for subject of the same age) and T-score (comparison to young adult subjects, which reflects

<table>
<thead>
<tr>
<th>Table 1 Causes of secondary osteoporosis.</th>
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<tr>
<td><strong>Endocrine diseases</strong></td>
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<td>Hypercortisolism</td>
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<td>Hypogonadism</td>
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<td>Hyperparathyroidism</td>
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<td>Prolactin-secreting pituitary adenomas</td>
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<td>Hyperthyroidism</td>
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<td>Insulin-dependent diabetes</td>
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<td>Acromegaly</td>
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<td><strong>Inflammatory and systemic diseases</strong></td>
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<tr>
<td>Chronic inflammatory rheumatoid diseases (rheumatoid arthritis, spondyloarthropathies)</td>
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<tr>
<td>Mastocytosis</td>
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<td><strong>Digestive disorders</strong></td>
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<td>Gastrectomy</td>
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<tr>
<td>Inflammatory enterocolopathy</td>
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<tr>
<td>Extended intestinal resections</td>
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<tr>
<td>Malabsorption, malnutrition</td>
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<tr>
<td>Chronic severe liver disease</td>
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<tr>
<td><strong>Neoplastic diseases</strong></td>
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<td>Multiple myeloma</td>
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<tr>
<td>Metastatic cancer</td>
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<tr>
<td>Chemotherapy for cancer</td>
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<tr>
<td><strong>Genetic disorders</strong></td>
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<tr>
<td>Lobstein disease (osteogenesis imperfecta)</td>
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<td>Connective tissue diseases (Ehlers-Danlos disease, Marfan syndrome, elastorrhexis)</td>
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<tr>
<td>Homocystinuria</td>
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<tr>
<td>Hemochromatosis</td>
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<tr>
<td><strong>Drugs</strong></td>
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<tr>
<td>Corticosteroids (no consensus on inhaled corticosteroids)</td>
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<tr>
<td>GnRH antagonists</td>
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<tr>
<td>Aromatase inhibitors</td>
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<tr>
<td>High doses of thyroid hormones (TSH suppressing)</td>
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<td>Extended heparin treatment</td>
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<tr>
<td>Chemotherapy for cancer</td>
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<tr>
<td>Lithium</td>
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<tr>
<td>Antidepressants, proton pump inhibitors (?)</td>
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<tr>
<th>Table 2 Risk factors for fragility fractures (from the French AFSSAPS).</th>
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<tbody>
<tr>
<td>Age</td>
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<tr>
<td>T-score for the lumbar spine and/or proximal femur</td>
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<tr>
<td>Personal history of fracture</td>
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<tr>
<td>Current or previous corticosteroid treatment</td>
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<tr>
<td>History of proximal femur fracture in first-degree relatives</td>
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<tr>
<td>Low body weight (body mass index &lt; 19 kg/m²)</td>
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<tr>
<td>Reduction in visual acuity</td>
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<tr>
<td>Neuromuscular or orthopaedic problems</td>
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<td>Smoking</td>
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Medical management following an osteoporotic fracture

Previously mentioned factors (Fig. 2). Its main benefit is that it calculates individual fracture risk as a function of the pre-existing factors. The drawback of this approach is that the risk is not quantified (or even estimated). Reimbursement conditions could be determined by peak bone mass). By convention, osteoporosis is defined by the WHO as a T-score (at the lumbar spine or hip) lower than −2.5 [20]; osteopenia is present when the score is between −1 and −2.5 standard deviation. Normal subjects have a T-score above −1 at both sites (Table 3 and Fig. 1).

To be reliable, this measurement must have been carried out by a trained operator and performed on a scanner subject to regular quality control. Knowledge of interpretation traps is needed to avoid wrongly classifying a patient into an inappropriate bone status category. It would be ridiculous to interpret DEXA results without knowing the patient’s clinical context.

Evaluation of individual fracture risk
The drawback of this approach is that the risk is not quantified on an individual level. A new tool, FRAX®, created from multiple international databases at the request of the WHO, calculates individual fracture risk as a function of the previously mentioned factors (Fig. 2). Its main benefit is that risk is quantified by determining individual probability of fracture at 10 years, either for “major” osteoporotic fractures (femoral neck, vertebra, wrist, proximal humerus) or specifically for the femoral neck.

However this tool has certain limitations that should be mentioned. First, from a technical point of view, the bone mineral density measurement site chosen for the FRAX® is the femoral neck. There is often a conflict between the femoral neck values and typically lower spine values, especially in younger menopausal women. The femoral neck measurement is also less reproducible. Second, the fracture history entered into the FRAX® does not take into account the type of fracture (vertebral and hip fractures are known to have a greater effect on the future risk of a new fracture) nor the number of previous fractures (correlated to the risk of future fractures, especially for vertebral fractures). The cumulative corticosteroid dose is not considered, which limits the use of the FRAX® in patients with chronic inflammatory diseases. Finally, the interpretation of the results brings up problems related to treatment decision thresholds. This tool is now mostly used in pharmacoeconomic studies to establish the cost-efficacy threshold for each age range.

Table 3  DEXA indications that are approved by the French HAS and reimbursed by the French National Health Insurance since 2006.

Indications for the general population
Disease or treatment that induces osteoporosis
On-going « systemic corticosteroid therapy », prescribed for at least three consecutive months, at a dose equal to or above 7.5 mg/day of prednisone equivalent (preferably at the start of treatment)
Documented history of long-standing hypogonadism (including surgical [orchidectomy, ovariectomy] or drug-induced [extended GnRH agonist treatment] androgen or oestrogen deprivation), untreated progressive hyperthyroidism, hyperadrenocorticism, primary hyperparathyroidism, osteogenesis imperfecta

Addition indications in menopausal women
History of « systemic corticosteroid therapy », prescribed for at least three consecutive months, at a dose equal to or above 7.5 mg/day of prednisone equivalent
Body Mass Index (BMI) < 19
History of femoral neck fracture without major trauma in a first-degree relative
Menopause before 40 years of age, independent of the reason

When osteoporosis signs are present, current recommendations advocate the investigation of a disease responsible for secondary osteoporosis, or a tumour or traumatic cause for the fracture. No matter the context, DEXA is only indicated if the results of the scan can a priori lead to a change in patient management. DEXA is not indicated if the woman is undergoing hormone replacement therapy (HRT) with doses that are recommended to prevent osteoporosis (and not only to relieve hot flash symptoms).

Table 4  Diagnostic classification of osteoporosis with DEXA.

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
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<tr>
<td>Normal</td>
<td>BMD less than 1 SD below a young adult (T-score &gt; −1 SD)</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>BMD between −1 and −2.5 SD that of a young adult</td>
</tr>
<tr>
<td>Osteoporosis</td>
<td>BMD more than 2.5 SD below that of a young adult</td>
</tr>
<tr>
<td>Confirmed osteoporosis</td>
<td>BMD more than 2.5 SD below that of a young adult and presence of one or more fractures (T-score &lt; −2.5 SD + fractures)</td>
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Figure 1  Change in bone mineral density with age. An average curve with +1 and −1 standard deviation boundaries is shown. Normal (green), osteopenia (orange) and osteoporosis (red) areas are shown. The result of a female patient nearly 70 years old is shown on this curve to demonstrate how to calculate the scores: for this patient, the Z-score is −1 and T-score is −2.6.
the results of these studies. The evaluation of individual risk will always be estimated from epidemiological data [21]. Despite its limitations, the FRAX tool is an important step towards an objective approach to the evaluation of fracture risk in an osteoporotic patient.

**How about biological markers of bone remodeling?**

Biological bone markers such as total and bone-specific alkaline phosphatase, osteocalcin (for formation) and type I collagen fragments (CTX for resorption) are reimbursed by the French Social Security. However, their role in the diagnosis and evaluation of fracture risk has not yet been determined [22]. Insufficient published data exists to show that these tests are clinically useful to monitor treatment efficacy. They could however identify patients who are not taking their drugs or who have absorption problems (especially for oral bisphosphonates), as these tests are more sensitive and able to detect changes earlier than DEXA. After a fracture, the level of bone remodeling markers generally cannot be interpreted because of increases related to the fracture callus. These levels can be elevated for 6 to 12 months.

**The risk of falling should also be evaluated**

This evaluation should be done during every initial survey of an osteoporotic patient, especially if a fracture has already occurred. Falling is a very common contributing or causal factor. Many risk factors for falling have been identified in epidemiological studies and two are on the French AFSSAPS list of fracture risk factors: neuromuscular and orthopaedic problems and reduction in visual acuity. Balance problems (especially iatrogenic) and obstacles at home are often the cause of falls and fractures, especially in elderly subjects. The use of preventative measures to correct these factors will help to diminish fracture risk.

**Bone quality, the black hole of osteoporosis evaluation**

Bone quality is not only determined by its mineral density, but its structure (micro-architecture of the trabecular network, thickness of bone cortex, amount of mineralization in the protein matrix, etc.); both determine bone mechanical properties [23]. These qualitative parameters seem to be related to fracture risk. Non-invasive methods to evaluate bone quality (micro CT, high-resolution MRI, etc.) are being intensively researched but are not yet validated.

**Treatment methods**

The goal of osteoporosis treatment in a patient who has had a fracture is to reduce the risk of a new fracture, either vertebral or peripheral.

There have been significant advances in the treatment of osteoporosis in the past 15 years. An increasing number of molecules with various mechanisms of action, proven efficacy, a good efficacy/safety ratio are now available to be used within the framework of the French AFSSAPS recommendations, which are currently being updated. The choice of the first drug, monitoring and duration of treatment and questions related to observance (adherence and persistence) are still being debated. Treatment strategies require that the bone deficit be treated with health, diet and drugs measures and that falls in older subjects be prevented.
Healthy and diet measures

Calcium and vitamin D deficiencies, very common in the French population, must be systematically identified with a validated self-questionnaire (Fardellone questionnaire) on the dietary intake of calcium and through an assay of the stored form of vitamin D, 25 hydroxy-vitamin D (25 OH-D), preferably the sum of 25 OH-D2 and 25 OH-D3.

Vitamin D deficiency is very common in the elderly; this high prevalence has been known for a long time and is associated with a decrease in BMD (particularly because of a parathyroid reaction) and increase in the risk of falling and fracture, because of the important role of vitamin D in muscle metabolism. This is particularly evident in patients who have recently suffered a femoral neck fracture [24,25].

These observations are a powerful reason to screen for vitamin D insufficiency or deficiency and to correct it. Any insufficiency or deficiency must be addressed by changing the diet or with an appropriate calcium and vitamin D supplement. The target concentration of 25 OH-D is 75 nmol/L (30 ng/mL); a vitamin D insufficiency and deficiency is defined as serum concentrations lower than 50 nmol/L (20 ng/mL) and 25 nmol/L (10 ng/mL), respectively. The preferred and simplest way to address the problem is through the intake of vitamin D3 of animal origin (cholecalciferol). Different treatment schemes are possible, without one being superior [26]. Vitamin D is available either in ampules that can be taken orally or injected or as a combination of vitamin D with calcium or a bisphosphonate. The recommended daily intake of vitamin D is between 800 and 1000 IU, once the initial insufficiency or deficiency is corrected. No supplementation approach has been shown to be superior in cases of deficiency. To ensure that the correction is adequate, an 25 OH-D assay can be performed one week after the last ampule is taken [26]. Maintenance treatment is absolutely necessary to keep 25 OH-D levels above 30 mg/mL. Adherence can be improved by administering either 100 000 IU of D3 every 2 or 3 months, or 800 to 1600 IU of D3 every day. There is no risk of overdose with these doses of vitamin D.

Regular physical activity is recommended to maintain satisfactory bone mass. It also has a beneficial effect on balance, muscle tone and an active role in preventing falls. The repletion of vitamin D also improves muscle function and significantly reduce the risk of falls [27]. The recommended exercise regime is a weight-bearing activity that involves ground impacts, for example walking, for about 30 to 60 minutes per day. In elderly people and those with a high risk of falling (such as institutionalized people for example), a hip protector could reduce the risk of proximal femur fracture. Finally, removing modifiable extrinsic risk factors such as smoking and excessive alcohol intake can be beneficial.

Drug therapy

An indication for drug treatment is always the result of the evaluation of individual risk factors, due to the reoccurrence of a fracture, through the identification of clinical factors, along with the interpretation of the DEXA scan and potentially supported by the FRAX tool mentioned above. The goal of treatment is to prevent fractures. This treatment should be considered as the management of a chronic disease. It is important to determine the patient’s motivation and to heighten their awareness of problems with treatment adherence, which can limit treatment efficacy [28]. Almost one of two patients stops their treatment after 6 to 12 months. Currently authorized drug classes are divided according to their action on osteoclast resorption, osteoblast formation or both.

Antiresorption treatments

Selective estrogen receptor modulators (SERM)

Only raloxifen (Evista®, Optruma®) is currently available for the treatment of postmenopausal osteoporosis. It slows bone remodeling and prevents lumbar and femur bone loss in women who have recently entered menopause. Increases in lumbar and femoral BMD are modest as the woman is further past menopause. Raloxifen (60 mg per day) reduces the risk of vertebral fractures but not peripheral fractures, such as the femoral neck [29]. Thus it is mainly indicated in female patients with an elevated risk of vertebral fracture but no significant risk of femoral neck fracture, essentially menopausal patients under 70—72 years of age. The risk of proximal femur fracture increases rapidly above this age, making it preferable to choose another type of drug. Systemic safety is good. Hot flashes and leg cramps can be uncomfortable for the patient at the start of treatment.

A recent study has shown a preventive effect on estrogen-receptor dependent invasive breast cancer (HR = 0.56 [95% CI: 0.38—0.83]). Conversely, there were no beneficial cardiovascular effects in terms of heart disease [30] and even a tendency towards increased mortality due to strokes (HR = 1.49 [95% CI: 1.00—2.24]) and increased risk of thromboembolism (HR = 1.44 [95% CI: 1.06—1.95]). There are no effects on the endometrium.

Bisphosphonates

Bisphosphonates are stable pyrophosphate analogues that incorporate and accumulate easily in the bone matrix. They are mainly anti-osteoclastic agents. There are five commercially available bisphosphonates. Etidronate (Didronel®) has practically no usage as it has the lowest level of evidence of efficacy. Risedronate (Actonel®) and alendronate (Fosamax®) taken daily (5 mg and 10 mg respectively), especially weekly (35 mg and 70 mg respectively) or more recently monthly (75 mg risedronate on two consecutive days, once per month) reduce the risk of vertebral and peripheral fractures [29]. Ibandronate (Bonviva®), at a monthly dosage of 150 mg or slow intravenous administration (20 to 30 seconds) of 3 mg every 3 months, is indicated only for the prevention of vertebral fractures. Zoledronic acid (Aclasta®), administered as a rapid infusion (15 to 20 minutes) once per year, prevents vertebral and non-vertebral fractures, including the hip. This bisphosphonate is the only drug to be evaluated in an elderly population (men and women with an average age of nearly 75 years) with a recent femoral neck fracture. The treatment reduced fracture risk by 35%, fracture risk of the contralateral femoral neck by 30% and also reduced mortality by 28% in these very frail patients [31].

The number of available administration modes makes it easier to choose something that is convenient for the
patient, thus improving adherence. Similarly, combinations of alendronate with vitamin D (Fosavance®, Adrovance®) can simplify the treatment plan.

Safety is generally good, but absorption in the gut is poor and can lead to oesophagitis. This mean that the drug must be taken while fasting, for example 30 minutes before breakfast, with a large glass of poorly mineralized or non-mineralized water, without lying down or bending down, to avoid reflux of the tablet into the oesophagus. Cases of jaw osteonecrosis have been reported with bisphosphonates in very rare cases. These observations are mainly for bisphosphonates administered intravenously on a monthly schedule for the treatment of malignant osteolysis (meyoloma, metastasis). The risk is extremely low in osteoporotic people. However, it is justified to verify that an oral-dental examination was performed the year before the treatment and to perform any required invasive dental care such as extraction, before the bisphosphonate treatment is started.

Bone formation treatments

Teriparatide (Forsteo®)
This is a 1–34 peptide fragment of human parathyroid hormone. This teriparatide is a powerful bone-forming agent that is administered by daily subcutaneous injection. The availability of a prefilled injection pen makes it easier to use, as patients can perform the injections themselves. Administration of this treatment in menopausal women with severe osteoporosis prevents about two-thirds of vertebral fractures. It also prevents peripheral fractures, with a lower level of evidence, however no effect on femoral neck fractures has been demonstrated [29].

This restricted-use drug (special prescription) is indicated for 18 months in men and women with severe osteoporosis or glucocorticoid-induced osteoporosis, and only reimbursed in patients with at least two previous vertebral fractures and a low bone mineral density (T-score < −2.5).

Decoupling agents
Strontium ranelate (Protelos®)
Strontium ranelate is unique in that it simultaneously improves bone formation and reduces bone resorption, by decoupling bone remodeling in favour of bone anabolism. Strontium ranelate reduces the risk of vertebral and peripheral fractures in menopausal women and reduces the risk of hip fracture in a sub-group of women above 74 years of age with low bone density [32]. This drug has the greatest level of evidence in women above 80 years of age for all types of fractures.

It is taken daily as a 2 g powder packet that is dissolved in a glass of water. Because of its poor bio-availability, it should be taken in the evening before bed, well after meals. Safety is good, other than the occasional headache or diarrhea at the start of treatment. A slight increase in the risk of thromboembolism has been reported; this is not a contraindication but a precaution when used in patients with a risk or history of thrombosis. However, a very recent reevaluation of the drug by the French Drug Agency (AFSSAPS) has led to the suspension of authorization of strontium ranelate in elderly patients over 80 years, due to their higher risk of thromboembolic disease. A few cases of hypersensitivity with severe systemic affection (DRESS syndrome) were reported in late 2007. These occurred at the start of treatment (first six weeks). The treatment should be immediately stopped if a suspicious skin rash appears.

Role of hormonal treatment in menopause

Hormonal treatment during menopause slows or stops bone loss due to oestrogen deficiency. The inhibitory action of oestrogens on osteoclasts slows down bone remodeling, however this effect is lost when treatment is stopped. To prevent fractures, the dose is higher than the ones used to control the hot flash symptoms of menopause.

Recent data has shown increased mammary, venous thromboembolic, coronary artery and cerebral vascular risk, which has raised questions about the multiple indications for this treatment. Hormonal treatment during menopause is indicated for significant hot flash symptoms, and prescription duration is adapted to changes in these symptoms. With the availability of effective treatment alternatives, this is no longer the first line treatment for post-menopausal osteoporosis [33].

Future treatments

Denosumab (RANKL antibody)
This new drug is the first to bridge osteoporosis and biotherapeutics. Denosumab blocks the action of RANKL (RANK ligand, an osteoblast factor that drives osteoclast differentiation and resorption activity) and leads to a reduction in bone resorption. Denosumab reduces the risk of vertebral fractures, non-vertebral fractures and especially femoral neck fractures [34]. It is not yet commercialized in France.

Anti-cathepsin K
Cathepsin K is secreted by osteoclasts into the resorption pit and is a key bone resorption enzyme. Blocking the action of this enzyme slows down bone loss. A very specific inhibitor is currently being developed for osteoporosis, with promising preliminary data.

Osteoblast differentiation promoting agents
Full length PTH (1–84) is being evaluated as an alternative to the teriparatide. Not yet commercialized in France, it has shown to be effective against vertebral fracture and could also be effective with weekly sub-cutaneous administration instead of daily.

Osteoblast growth factors such as IGF, BMP and FGF are interesting bone anabolic treatment approaches. Activation of the Wnt/β-catenin pathway is another potential approach, either by preventing β-catenin degradation (with lithium for example) or by blocking its inhibitors (anti-Dkk1, anti-sclerostin, etc.).
Medical management following an osteoporotic fracture

Table 5 Level of proof for the efficacy of osteoporosis drugs relative to vertebral, non-vertebral and hip fractures.

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<th>Efficacy relative to vertebral fractures</th>
<th>Efficacy relative to peripheral fractures</th>
<th>Efficacy relative to hip fractures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium + vitamin D</td>
<td>ND (−?)</td>
<td>+/−</td>
<td>++/−</td>
</tr>
<tr>
<td>HRTb</td>
<td>+</td>
<td>−</td>
<td>+</td>
</tr>
<tr>
<td>Raloxifen</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Alendronate, risedronate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Ibandronate</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Zoledronic acid</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Teriparatide</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>PTH 1—84c</td>
<td>+</td>
<td>−</td>
<td>−</td>
</tr>
<tr>
<td>Strontium ranelate</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Denosumabc</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

a Low level of proof, studies are contradictory. Using this treatment in isolation is not recommended.
b Not indicated to prevent or treat osteoporosis in France.
c Drug has marketing approval, but is not commercialized in France.
d Post-hoc analysis on a sub-group of women above 74 years of age with a hip BMD T-score < −2.5.
e Does not have marketing approval yet, but recent data published.

Treatment strategies: who should be treated, with which drug and for how long?

Which patients should be treated?

In the context of osteoporosis management in a male or female patient with a recent fragility fracture and osteoporosis, treatment indications are broad but the decision is always based on clinical judgment. Any patient above 60 years of age with a history of significant fracture (vertebra, proximal femur, humerus) is considered as a treatment candidate if the fragility state is confirmed by DEXA scan (osteoporosis or osteopenia). With a wrist or other (rib, pelvis, tibia, metatarsal, etc.) fracture, treatment is indicated in cases of osteoporosis confirmed by DEXA ("all the more" if the T score is very low) and the presence of other fracture risk factors. This is a situation where the FRAX could be used to guide the clinician’s decision, based on the risk score provided by this tool. However, the intervention thresholds have not yet been validated in France (but will be proposed soon in the frame of the revised guidelines). In younger persons, fracture risk is low and the treatment indication must be carefully weighed.

Choice of treatment

As with most chronic diseases, osteoporosis treatment involves an overall pre-treatment evaluation to educate the patients, discuss with them the most relevant options and agree on the final decision, when possible [35].

In 2006, the French AFSSAPS published good practice recommendations for the therapeutic management of osteoporosis as a function of different potential clinical situations. This document is available on the website of the French AFSSAPS. The proposals are based on the existence of an associated fracture (excluding skull, cervical spine, hand and toe fractures), age, bone density and other fracture risk factors. The recommendations are currently being updated to take into account new treatments and the individual fracture risk evaluation provided by the FRAX tool.

Table 5 summarizes the efficacy of current treatments in the prevention of vertebral, peripheral or proximal femur fractures. The choice must also take into account the motivation for the treatment (long term and with no immediately apparent benefit), practical methods for drug delivery based on patient preference, medical history, and compare these with the risk profile of the osteoporosis drugs. Raloxifen has the added benefit of preventing breast cancer, even in high-risk women [30], but it is contraindicated when a history of severe thromboembolism exists. Strontium ranelate must be used with care under these circumstances. In elderly patients, fragile and dependent, annual zoledronic acid infusion ensures the treatment by avoiding the limitations and uncertainties of oral administration. All treatments must be avoided in patients with severe kidney failure (clearance below 30 mL/min), however it will be possible to use denosumab in the future in these patients.

In women above 75 years of age who have a rapidly increasing risk of femoral neck fracture, raloxifen and ibandronate should be avoided as they do not address this risk.

Finally, regulatory aspects must be considered; the teriparatide is only reimbursed in patients with at least two vertebral fractures. Prescribing it outside this framework should be avoided as its high price requires good reimbursement coverage.

What length of treatment?

The duration of osteoporosis treatments is not regulated. It is based on observational efficacy and safety data with the maximum follow-up occurring during open-label trials. However we need to remember that this disease must be managed over the long-term, which implies periodic reevaluation to monitor the risk of fracture, especially if treatment has been interrupted [36]. Raloxifen can be prescribed without issue for 10 years or more. The logical approach is to stop when the risk of non-vertebral fractures
begins to increase, thus after 70 to 74 years of age. Long-term data (up to 10 years) with the original bisphosphonates have been published and demonstrated good safety, which justifies this length of treatment, even if some prefer a shorter treatment period such as five years. Indeed, the recently reported “atypical” subtrochanteric or diaphyseal femoral fracture during long-term bisphosphonate treatment occur after a mean duration of five to seven years of exposure to the drug. For the teriparatide, the maximum treatment period is set according to the conditions of use: currently 18 months and probably 24 months soon. Since strontium ranelate has only been commercially available since 2007, the question is not really relevant; however 5-year efficacy and 8-year safety data are encouraging.

These theoretical treatments durations must be put into perspective relative to poor treatment adherence, which is currently the greatest barrier to the efficacy of these treatments. Monitoring osteoporotic patients is essential to verify and emphasize the importance of treatment adherence to optimize the chances of success.

Treatment monitoring and patient follow-up

Monitoring is an unavoidable practical challenge because there are no markers for short-term treatment efficacy.

Clinical monitoring must be linked, consultation after consultation, to verify adherence and safety of the prescribed treatment and any supplements, observance of health and diet rules and the absence of new fractures. A reduction of 2 cm or more in height between two visits six months apart cannot be ignored and should lead to a request for thoracic and lumbar spine x-rays to look for a vertebral fracture [37]. The occurrence of a fracture during treatment should lead the physician to ask multiple questions: poor treatment adherence or poor treatment intake (e.g. oral bisphosphonate taken during meals or with calcium) or treatment failure? If poor adherence to an oral treatment is evident, an intermittent parenteral treatment could be solution. Treatment failure is defined as the occurrence of a non-traumatic fracture beyond the first year of taking the same osteoporosis drug. The treatment must be changed.

DEXA measurement is not indicated to monitor an anti-osteoclast treatment, because a measurement taken within 2 years of treatment initiation has little chance of detecting a significant change. The rapid increase in bone mineral density induced by the teriparatide or strontium ranelate could allow an early evaluation to be considered, for example after the first year of treatment, however this indication is not approved in the French HAS reimbursement rules.

The role of biochemical markers of bone remodeling as a monitoring tool has not been established, however in certain cases it could identify patients with adherence or absorption problems.

Conclusions

Considerable progress has been made in the diagnostic and therapeutic management of osteoporosis. The primary goal is to treat patients with a history of fragility fractures, which would certainly reduce the medical, social, psychological and personal impact of osteoporotic fractures. Recent data suggest that better access to DEXA for diagnosis and the availability of effective treatments could start to shift the incidence curves for certain osteoporotic fractures — this is an important issue for us in the next 20 to 50 years!

Disclosure of interest

Philippe Orcel discloses the following conflict of interest:

- long-term or on-going relationships:
  - personal payment for research, scientific evaluation and consulting activities: Servier,
  - consultant, member of an expert group or equivalent: Amgen, Servier, MSD, Novartis, Lilly, Roche, GSK,
  - contract or research grant: Novartis;
- limited subsidies:
  - clinical and preclinical trials and scientific work, acting as the principal investigator for a single-centre study, investigator coordinator or primary researcher: Amgen, Servier, Novartis,
  - clinical and preclinical trials and scientific work, as a co-investigator or non-primary researcher: Procter & Gamble, SanofiAventis, Novartis, Lilly,
  - expert reports or preparation of promotional articles: Servier, Novartis, Lilly,
  - consulting activities: Amgen, Servier, MSD, Novartis, Lilly, Roche, GSK,
  - teaching activities as a contributor to various conferences, symposiums, public meetings: Amgen, Servier, Procter & Gamble, SanofiAventis, MSD, Novartis, Lilly, Roche, GSK;
- indirect interests
  - payments into a facility budget that you are responsible for: Servier, Procter & Gamble, SanofiAventis, MSD, Novartis, Lilly.

Thomas Funck Brentano declares that he have no conflicts of interest concerning this article.

References


