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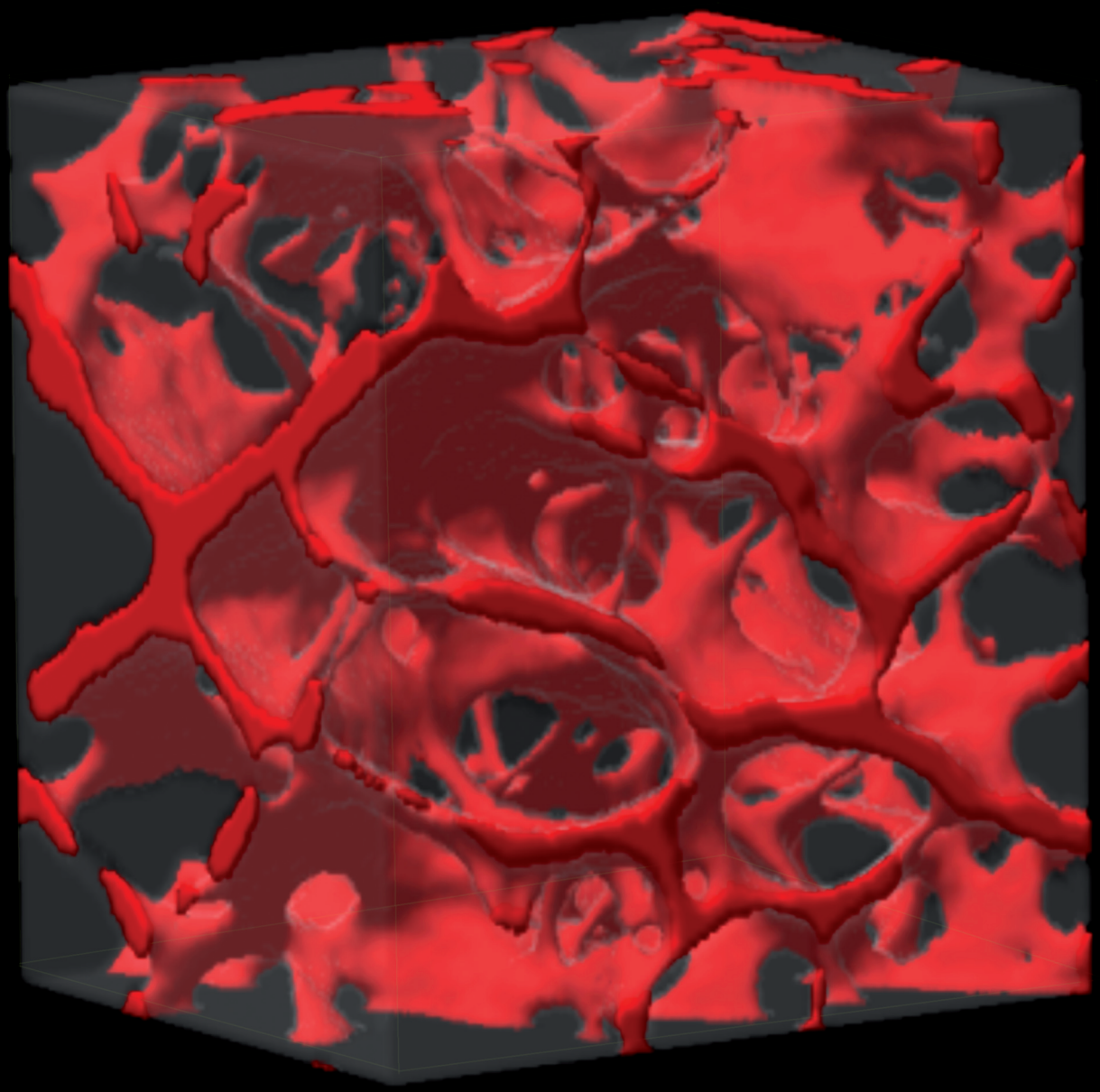

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PROBLEMAS Y SOLUCIONES EN EL ABORDAJE DE LA OSTEOPOROSIS

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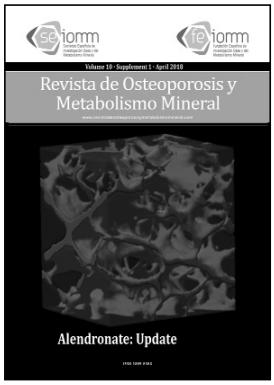

Our cover
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SUMMARY

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Osteoporosis: Concept. Pathophysiology. Clinical. Epidemiology

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Concept

Osteoporosis is the most common bone metabolic disease. It is generally defined as "systemic skeletal disease characterized by decreased bone strength with consequent increase in bone fragility and susceptibility to fractures"[1]. The essential elements of this definition are low bone mass and microarchitectural alteration, which distinguish osteoporosis from other bone diseases. The alteration of the microarchitecture is characterized by the loss, thinning and lack of connection between the bony trabeculae, together with a series of factors, such as alterations in the bone remodeling and the bone geometry itself, among others that have been grouped under the concept of bone quality[2]. On the whole, osteoporosis involves a deterioration of the structural integrity of the bone which favors skeletal fragility and causes increased risk of fractures (fx).

The World Health Organization (WHO) established an operational definition based on bone mineral density (BMD) determination in any skeletal region for white women. Thus, normal BMD values were established to those higher than -1 standard deviation (SD) in relation to the mean of young adults.

Normal (T-score > of -1); osteopenia BMD values between -1 and -2.5 SD (T-score between -1 and -2.5); osteoporosis BMD values lower than -2.5 SD (T-score below -2.5) and established osteoporosis when, together with the previous conditions, one or more osteoporotic fx is associated[3].

It is important to consider that the WHO criteria should be used preferably to ascertain the epidemiology of osteoporosis and not to apply them in isolation or to indicate preventive and therapeutic measures. Although not perfect, the definition of osteoporosis according to BMD is valid, since there is a strong association between BMD and fracture risk. Prospective studies show that the decrease of a SD in BMD increases the risk of fracture between 50 and 160% (relative risk: 1.5-2.6)[4].

Pathophysiology

Throughout life, bone tissue is being formed and destroyed continuously, a process known as bone remodeling, which occurs in the so-called remodeling units. Among the functions of bone remodeling are replacing old bone with new, and therefore more resistant, and participating in bone mineral homeostasis.

Osteoporosis is the result of an alteration in bone remodeling that is always due to an imbalance between the formation and bone resorption, with predominance of the latter, which leads to both the loss of bone mass and the development of microstructural alterations that we have called bone quality[2].

Bone remodeling is a complex process involving mechanical and humoral factors (hormones: PTH, calcitonin, vitamin D, sex hormones, estrogens, androgens, thyroid hormones, growth hormone and corticosteroids), as well as local factors (IL-1, IL-6, TNF, M-CSF, RANKL, TGF, OPG, IGFs... etc.) and bone cells: osteoblasts, osteoclasts and osteocytes. Alterations in bone remodeling can lead to a negative balance of bone that will produce bone loss and the development of osteoporosis[5-8].

The relationship between osteoblasts and osteoclasts is established by two different molecular systems that, however, contribute to the same final effect. One of them is the M-CSF growth factor, for which the osteoclasts have the c-FSM receptor. M-CSF is soluble, and therefore secreted by osteoclasts or their precursors and has an osteoclast-stimulating effect.

The other is the RANK-RANKL-OPG system[9-10], mentioned above. RANK (receptor for activation of nuclear factor κ B [NFκB]) is a receptor of the TNFR family present in osteoclasts, to which the RANKL (or ligand of RANK, of the TNF family) present in the membrane of osteoblast/medullary stroma cells. As a consequence of this union, the proliferation and activity of the osteoclasts increases, while their apoptosis decreases. OPG (osteo-

protegerin) is produced in the osteoblast, also a member of the TNFR family. Its ligand is RANKL itself, so it can be said that it stands between it and the RANK, thus preventing its contact. Therefore, the osteoblast produces both the activator of the osteoclasts and a substance that neutralizes this activator.

Bone quality includes a group of factors other than bone mass, which also determine bone fragility. These include structural aspects of the bone (such as the size and angle of the femoral neck) and microscopic or microstructural aspects (such as the connection between the trabeculae and the thickness thereof, as well as the mineralization of the bone, the microscopic damage that could have, the quality of collagen and osteocytes)[11].

Clinical aspects: Fractures

Osteoporosis is a very common disease that affects 150-200 million people in the world. Approximately half of these patients belong to developed countries such as North America, Europe and Japan. In general, it is estimated that around 33% of women 50 and older will suffer from osteoporosis.

The prevalence of osteoporosis increases with age. In women between 20-44 years, the prevalence of the disease is only 0.3% while among women 70-80 years of age, the prevalence is 40%. In men, the prevalence figures are lower. Among women aged 70-80 years, only 11.3% had densitometric osteoporosis values in the lumbar spine and 2.6% in the proximal extremity of the femur[12].

As a disease, osteoporosis is asymptomatic, with fx and its complications being the only clinical manifestations of the disease[13]. The fx of the proximal extremity of the femur, vertebra, humerus, ribs and distal extremity of the radius or fx of Colles are considered to be typically osteoporotic[14], although any fx can be produced with the exception of skull fractures.

Clinically, peripheral fx is the same as fx of the same non-osteoporotic location[13,14]. What distinguishes them, fundamentally, is the fact that osteoporotic fx occurs in the face of minor trauma (typically, simple fall from the standing position). For the rest, the patient also presents pain, functional limitation and deformity.

Epidemiology of fragility fractures

The fx constitute the clinical complication of osteoporosis. The risk of suffering a fx from 50 years on ranges in women between 39-53%, and between 13-22% in men, depending on the country under study.

The vertebral fx are the most common in patients with osteoporosis[15]. It is estimated that around 25 percent of women over 50 years of age will suffer one or more vertebral osteoporotic fx. The risk of vertebral fx for men is around 5.4%. Its prevalence in Spain is estimated between 17% and 23% in women over 50 years of age and somewhat less in men of the same age[16]. These fx can be asymptomatic, then being diagnosed accidentally when a chest x-ray is done, or also produce pain or other complications. Some of these patients develop, after the initial episode, chronic pain that worsens with prolonged standing and improves with decubitus. In addition, the vertebral fx cause a reduction in height and an alteration of the static of the spine, with kyphosis, shortening of the trunk and rectification of the lumbar lordosis, depending on the location of the fractured vertebra.

The most severe osteoporotic fx is hip fx, which in most cases occurs after a fall. The global incidence of hip fx due to osteoporosis increases with age and it is estimated that its incidence is around 2/100,000 in people under 35 years and 3,000/100,000 in people over 85 years. This translates into approximately 40,000 hip fx a year due to osteoporosis[17].

The hip fx is a process that affects more women than men, the ratio between women and men is very variable in the different published series, ranging between 2 and 3.

The mortality after a hip fx is appreciable. The figures differ according to the populations studied, but range between 12% and 40% in the first year. Its incidence in Spain is estimated at around 220 cases per 100,000 inhabitants/year, although with regional variations[18]. The hip fx has repercussions that are immediate after the fx itself, such as surgery in 80% of cases and, in general, a long hospital stay. However, the repercussions of a hip fx are not limited to its hospital treatment, but the patients' quality of life deteriorates considerably. Thus, most have residual disability and a percentage of cases lose the ability to lead an independent life. Only one fifth of the patients who walked without help before the fx did so six months later. The prognosis depends, in part, on the functional capacity prior to fx.

Colles' Fx is very common, and up to 15% of women can present it during their lifetime. They present a different pattern of incidence compared with vertebral and hip fx. They predominate in the female sex in a proportion of 4:1, occurring 85% in women.

Although this fx is the least deteriorating of all osteoporotic fx, its morbidity is often underestimated. In the ECOSAP study conducted in our country[19], it was observed in an outpatient population of 5,195 women over 65 years of age that the forearm fracture was 33.7% of all the fx. Colles' fx can cause persistent pain, functional disability, neuropathy and post-traumatic arthritis, as well as being a significant risk factor for the future presentation of vertebral or hip fx.

Finally, the psychological and social impact that osteoporotic fx can engender must be taken into account. The development of depression, anxiety, fear of new fractures, and other emotional reactions are also important, and influence the recovery of patients.

To sum up, since osteoporosis is a disease closely linked to age, the demographic aging of Western countries suggests the problem will multiply. There seems to be an increase related to fac-

tors inherent in the changes in our standard of living. The incidence of fx will also increase in other areas of the planet, such as in Asia, where a large increase is expected in the 21st century[20].

Conflict of interests: The author declares that he has no conflicts of interest.

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SELF-ASSESSMENT TEST

1. Which of the following statements is not true?
   a. RANK is a receptor present in osteoclasts
   b. The binding of RANK and RANKL (RANK ligand) is inhibited by OPG
   c. The osteocyte regulates the synthesis of RANKL
   d. All the above is true

2. Which of the osteoporotic fractures (fx) is the most frequent in clinical practice?
   a. Vertebral fx
   b. Fx of the upper third of the humerus
   c. Fx of the distal extremity radio
   d. Hip fx

3. Which of the following statements is not true?
   a. The prevalence of osteoporosis increases with age
   b. The vertebral fracture can be asymptomatic
   c. Mortality after a hip fx is less than 10%
   d. Everything is true

Answer key on page 24

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Osteoporosis and Primary Care. How to assess the risk of fracture. Use of risk scales

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Introduction

Osteoporosis is a metabolic bone disease characterized by a low bone mass and a deterioration of the microstructure of the bone tissue that leads to an increase in bone fragility and consequently to an increased risk of fracture[1]. Its real incidence is difficult to calculate since it is a silent process until the appearance of the fracture. It is one of the most prevalent osteo-articular diseases in primary care consultations. Since in 1994 the World Health Organization defined the densitometric values of osteoporosis which have been widely used to identify the population susceptible to suffering a fragility fracture[2]. Currently, population screening strategies[3] are not recommended to identify patients with osteoporosis. Rather, a precautionary search is suggested in those subjects with a high risk of fracture[4]. In addition, in recent years the role of the exclusive assessment of bone mass to estimate the risk of fracture in patients has been questioned. Identifying these patients at risk to direct the necessary diagnostic and therapeutic options is one of our most difficult and controversial tasks.

Risk factors for fracture

One of the first steps is to ascertain the risk factors associated with the appearance of fractures. Classically they are divided into[5]:

- *Older*: those who present a relative risk twice or more higher than the population without risk factor. We can distinguish:

1. Age >65 years. With age, the risk of fractures increases, independently of other risk factors. For every decade the risk of fracture is multiplied by 1.5-2 times.
2. Personal history of fragility fracture.
3. Family history of hip fracture, particularly in the parents.
4. Body mass index lower than 19 Kg/m^2 or if there is a weight loss greater than 10% of adult weight.
5. Use of oral glucocorticoids (dose of 5 mg or more of prednisone, or equivalent, for three or more months).
6. Untreated primary ovarian failure or hypogonadism in man.
7. Frequent falls (two or more falls per year).
8. Other diseases such as hyperparathyroidism, eating disorders, chronic malnutrition and malabsorption disorders.

- *Minors*: those who present a relative risk between one and two times higher than the population without the risk factor. Among them are[5]:

1. Female sex.
2. Smoking.
3. Alcohol consumption of 3 or more basic units per day is associated with an increased risk of fracture.
4. Early menopause (before age 40).
5. Rheumatoid arthritis.
6. Type 1 diabetes is associated with a decrease in bone mass and an increased risk of fractures of any location.
7. Hyperthyroidism not corrected

In addition to these classic factors, the list of diseases (chronic liver disease, chronic renal failure, hypertension, diabetes mellitus type 2, etc.) and drugs (aromatase inhibitors, proton pump inhibitors and anticonvulsants, among others) associated with an increase in osteoporotic fracture risk has increased in recent years.

Assessment of fracture risk

Different primary care studies emphasize that in a high percentage of clinical records the risk factors are not correctly recorded[6], and when they are recorded they are not taken into account when requesting a densitometry[7].

We can assess the risk through a qualitative assessment (based on the number of risk factors present) or quantitative (through the use of fracture risk scales).

The 2010 National Health System guide[5] recommends a qualitative assessment and, in the case of two or more major risk factors, carry out a study of bone mass.

Different national and international clinical practice guidelines consider that the presence of a previous vertebral or hip fracture, or the presence of two or more fractures from other locations, are indicators of a high risk of fracture and, consequently, they are patients that must be treated[8-10].

In case of choosing to make a quantitative assessment, we have different scales: Index Fracture[11], Garvan[12,13], QFracture©[14] and FRAX©[15].

In a survey of primary care physicians in the Canary Islands, more than 75% of the physicians surveyed answered a qualitative assessment, based on the presence of risk factors, while 28.6% used risk scales regularly[16].

Use of risk scales

FRAX© is the most applicable scale. It allows us to estimate the absolute risk of fracture at 10 years through a quick and simple assessment of a few risk factors. Allows calculation with or without value of bone mass. One of the main drawbacks is that many variables are dichotomous, so that it does not consider, for example, the total number and location of previous fractures or the total cumulative dose of corticosteroids. Studies conducted in cohorts of Spanish patients observe that the FRAX© tool underestimates the risk of fractures, especially for major fractures[17,18].

Two calibrations of the FRAX© tool have been published for the Spanish population (Figure 1). The first of these[19] proposes as low risk a risk of major fractures of less than 3.6% and as a high risk >10%. The threshold sensitivity of 3.6% for diagnosing osteoporosis was 51%, the specificity 68%, the positive predictive value 20% and the negative predictive value 90%. The other calibration comes from the FRIDEX cohort[20]. This considers a risk of major fractures lower than 5% and high risk if >7.5% at risk. For these cut-off points the sensitivity is 40.8%, the specificity is 92.3%, the positive predictive value is 25.3% and the negative predictive value is 96%. Its discriminative capacity is similar to the exclusive assessment of the value of the bone mass, especially for femur fracture[21]. These cut-offs have been validated in an external cohort[22], although the low number of fractures observed and the fact that no data are available on what happens in patients at intermediate risk requires further studies.

Recent work done in 361 patients found that the predictive capacity of both cut points was similar to the qualitative assessment (presence of 2 or more major risk factors), with better values observed for the cutoff point >3.5% for the cut-off point ≥5%, when identifying high-risk patients against whom to request densitometry[23].

Although at international level different clinical practice guidelines recommend the assessment of fracture risk using FRAX©[8], at the national level there are few clinical practice guidelines that recommend its use when deciding which patients to direct diagnostic and therapeutic strategies, being the usual the non-recommendation of the Spanish version of FRAX©[24].

The Garvan scale only considers a low number of variables (age, sex, weight, number of previous fractures, number of previous falls and bone mineral density optionally). It has been validated for a sample of 121 Spanish patients; a cut-off point >18.5% had a sensitivity and specificity of 67%[25]. Further studies are needed to corroborate the predictive capacity of this cut-off point for the Spanish population.

QFracture© is a scale based on the database of primary care physicians in the United Kingdom. For its calculation, 25 variables are necessary, among them the previous falls (very important predictor of fractures) and new emerging risk factors. There is no published work that validates this scale for the Spanish population.

Conclusion

Osteoporosis is therefore a reason for consultation that is highly prevalent in primary care. Identification and assessment are required in those patients that present a high risk of fracture based on the presence of risk factors. Although we have different scales that provide information on the absolute risk of fractures, it is not advisable to use them for the Spanish population due to the limitations mentioned above. It would perhaps be more interesting to have a scale that would allow estimating the absolute risk for the Spanish population.

Conflict of interests: The author declares that he has no conflicts of interest.

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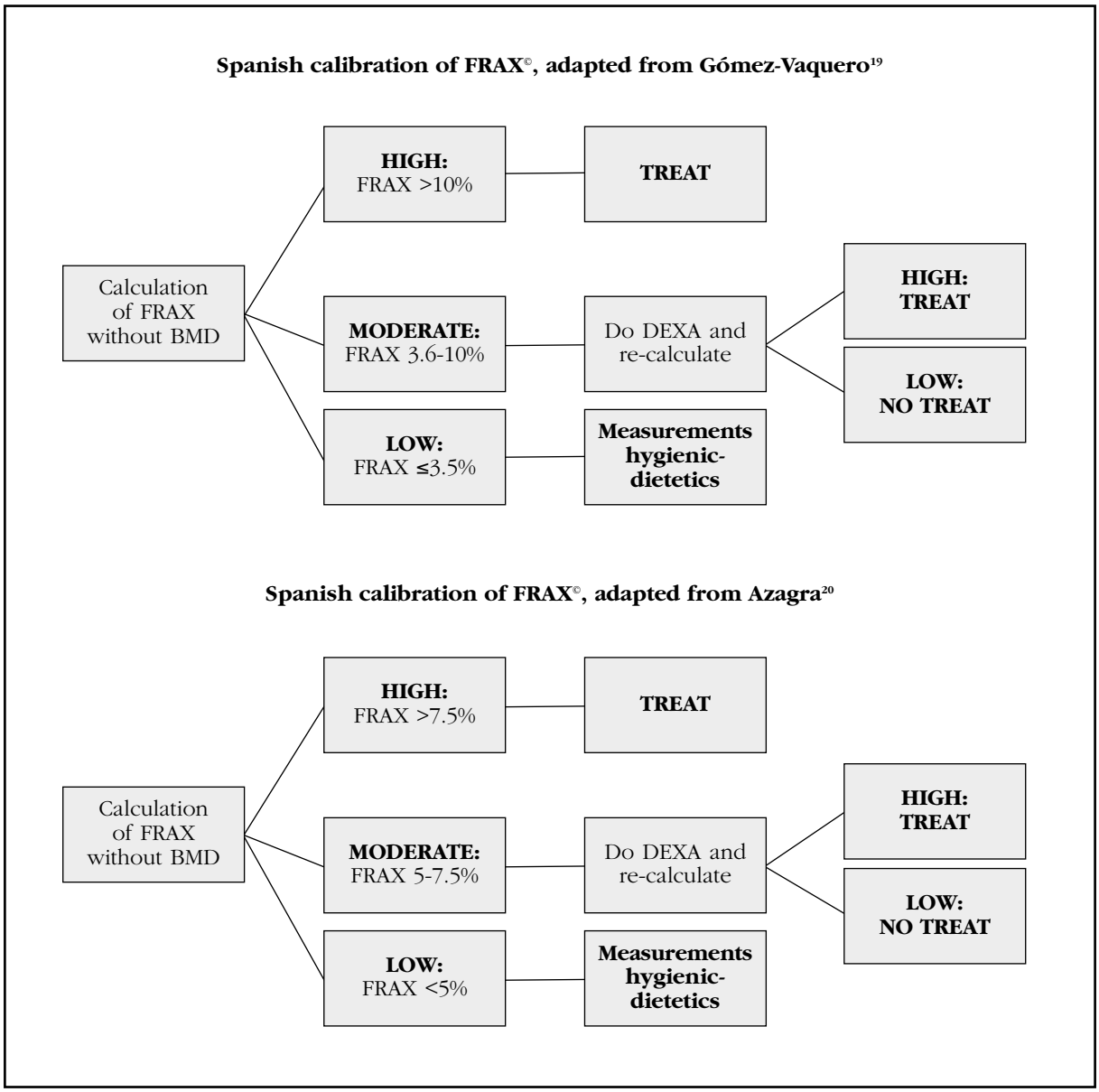
Figure 1. Calibration of the FRAX© scale for the Spanish population



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SELF-ASSESSMENT TEST

1. Which of these is not considered a major risk factor for fracture?
   a. Age 70 years
   b. BMI 20.5 Kg/m^2
   c. Femoral fracture in father
   d. Previous vertebral fracture

2. Which of these scales allows the estimation of the risk of fracture of the femur at 5 years?
   a. FRAX©
   b. QFracture
   c. Garvan
   d. B and C

3. According to the Spanish calibration of FRAX© of Azagra, indicate the correct one:
   a. A risk of major fracture without BMD of 3% recommends performing densitometry
   b. A risk of major fracture without BMD of 10% recommends assessing treatment
   c. A risk of major fracture without BMD of 6% recommends assessing treatment
   d. A risk of major fracture with BMD of 5% recommended treatment

Answer key on page 24

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Clinical practice guidelines concerning osteoporosis

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Introduction

Clinical practice guidelines (CPG) are a useful tool in medical practice, because they help guide the doctor in making decisions regarding a certain disease, based on a series of recommendations from the most up-to-date evidence available, combined with the consensus opinion of a group of experts on the subject[1].

CPGs not only provide knowledge and recommendations to the clinician in managing a specific ailment, but are also useful for the sustainability of health services, as costs soar in an increasingly aging and more technologically advanced society.

With CPG, heterogeneity in clinical practice is reduced, maintaining the balance between scientific evidence, economic efficiency and competent variability of the medical professional.

This is especially important in the case of osteoporosis. Patients often require multidisciplinary care, participating in different levels of care, so that it is necessary to try to achieve maximum homogeneity in the management of patients.

Despite being governed by a series of statements or recommendations, the CPGs do not have to limit the doctor's autonomy, as they are usually not binding. That is, they may not be followed in certain cases, if the patient's specific characteristics or conditions advise another action guideline. In other words, the CPG will not replace the clinical judgment of the doctor who treats the patient.

In short, CPGs aim to maintain the quality of care through the adequate use of available resources, avoiding clinical decisions that are not scientifically based and reducing the variability of the practice.

How are clinical practice guidelines developed?

A CPG is carried out in several stages:

1. *Justification, scope and objectives.* A document of the scope and objectives of the guide should be drafted. It must be clearly structured and include the justification for the preparation of the guide, its objectives, the description of the patient considered, the clinical aspects to be treated, the scope of application, the final users and those aspects that will not be included in the guide.

2. *Composition of the CPG working group.* To prepare a guide, a multidisciplinary working group is required, with the participation of all those involved in the process: clinical and methodological coordinators, members of the technical or methodological team, health and non-health professionals, expert collaborators and external reviewers. All personnel must make a declaration of possible conflicts of interest.

3. *Formulation of clinical questions.* A list of clinical questions that will be answered with scientific evidence should be made. The questions will be formulated whenever possible in a structured format (PICO: patient, intervention, comparator, outcome).

4. *Search and selection of evidence.* A CPG implies carrying out systematic and exhaustive searches, mainly by searching the large bibliographic databases, such as PubMed/MEDLINE, EMBASE, Web of Science, Scopus, Psycinfo or CINAHL.

5. *Evaluation and synthesis of the evidence.* Although the quality of the evidence is a continuous spectrum, GRADE (Grading of Recommendations Assessment, Development and Evaluation)[2], proposes a simple and explicit classification in four grades: high, moderate, low and very low. The quality of the evidence is determined based on 4 factors: methodological quality, coherence, relevance of the study and sufficiency of the data.

6. *Formulation of recommendations.* The drafting of a recommendation must be concise, clear (avoiding ambiguities) and easy to transfer to clinical practice. The recommended actions must be established with precision and the strength of the recommendation must be reflected by labels, numbers, letters and symbols. The Scottish

Intercollegiate Guidelines Network (SIGN) system is still widely used to establish grades of recommendation (Table 1)[3].

7. *External review and public exposure.* The validation of the CPG by agents who have not participated in its preparation is essential to ensure greater quality, trust and acceptance. External review and public exposure are two processes of external validation that complement each other.

8. *Edition of the CPG.* CPGs can have different versions and formats depending on the use that they want to give and the users to whom they are addressed: clinicians, managers or patients. In the CPG Program of the National Health System, the following versions are proposed: complete CPG, brief guide, information for patients/citizens, methodological material and digital support.

9. *Updating the CPG.* To be useful for the decision making of health professionals and citizens, the CPG must be kept up-to-date, and it is recommended that this update be done every 2 or 3 years.

What are the main CPGs on osteoporosis?

CPGs on osteoporosis usually make recommendations for the diagnosis or identification of patients with high risk of fracture and for treatment. In the diagnosis section, the importance of clinical fracture risk factors, including bone mineral density values, is usually reviewed. In the treatment section, CPGs usually review the evidence of each drug in both primary and secondary fracture prevention.

The IOF (International Osteoporosis Foundation) collects on its website a list of the majority of CPGs on European osteoporosis (https://www.Iofbonehealth.org/europe-guidelines) and other countries of the world.

In Spain there are several CPGs on osteoporosis at the national level, some of which are multidisciplinary, such as that of the SEIOMM (Spanish Society of Bone Research and Mineral Metabolism), and others more focused on a specific medical group, such as family medicine, internal medicine, rheumatology, endocrinology, gynecology, traumatology and geriatrics, etc…

Although each guide has its own distinctiveness, there are a series of recommendations that are repeated in all the guides and practically year after year, because some aspects of both osteoporosis diagnosis and treatment do not vary among countries or geographical areas. They change with the years.

Alendronate treatment in the CPGs

The SEIOMM's most recent CPG on osteoporosis was published in 2014 (with an update in 2015)[4]. This guide highlights the importance of age, sex, bone mineral density (BMD) and the personal history of fracture as the main risk factors for fracture, exactly the same risk factors of the 2003 SEIOMM CPG[5]. In the therapeutic recommendations section, there have been new developments, with the incorporation of new treatments and the disappearance of some others no longer on the market. However, the treatment of first choice in patients with osteoporosis is still alendronate.

In the 2003 guide, alendronate and risedronate were the only first-line treatments that were repeated in all patients (with and without fractures, over and under 70 years), on the basis that, as set out in that guideline, "alendronate has a positive effect on lumbar and femoral BMD, and decreases the risk of vertebral, non-vertebral and femur fracture (level of evidence 1a)". More than 10 years later, the GSE of SEIOMM continues to position oral bisphosphonates (specifically alendronate and risedronate) as first-line treatments. In this guide, it is said that "alendronate at a dose of 70 mg/week reduces vertebral fractures, non-vertebral fractures

Table 1. Degrees of recommendation according to the SIGN system

Degrees of recommendation	
A	At least one meta-analysis, systematic review or clinical trial classified as 1++ and directly applicable to the target population of the guideline; or a volume of scientific evidence composed of studies classified as 1+ and with great consistency among them
B	A volume of scientific evidence composed of studies classified as 2++, directly applicable to the target population of the guide and showing great consistency between them; or scientific evidence extrapolated from studies classified as 1++ or 1+
C	A volume of evidence composed of studies classified as 2+, directly applicable to the target population of the guide and showing great consistency between them; or scientific evidence extrapolated from studies classified as 2++
D	Scientific evidence level 3 or 4; or scientific evidence extrapolated from classified studies as 2+
Good clinical practice	
✓	Recommended practice, based on clinical experience and consensus of the group of experts

and hip fractures at around 45, 25-30 and 45-55%, respectively (evidence 1a)" (Figure 1).

Another guide of interesting national scope is the CPG on osteoporosis and prevention of fragility fractures in the SNS of the Ministry of Health[6]. In this guide, the effectiveness of alendronate in primary prevention of vertebral and secondary fracture of all fractures (vertebral, non-vertebral, hip and wrist) is highlighted from a meta-analysis[7].

Finally, there are two additional advantages to the efficacy of alendronate that are also repeated in the guidelines: safety and cost-effectiveness. Although some patients report gastrointestinal symptoms, alendronate is usually well tolerated. It is also the most economical osteoporosis treatment. According to a recent NICE publication (https://www.nice.org.uk/guidance/TA464/chapter/1-Recommendations), alendronate is cost-effective in any male or female with any risk factor for osteoporosis or of fracture and that present a FRAX value for main fracture >1%. In this regard, it should be noted that a cost-utility study carried out in Spain showed that the prevention of hip fracture with alendronate in osteoporotic women over 64 years is cost-effective in the long term (20 years), and particularly profitable in the 75-79-year age group[8].

Conflict of interests: The author declares that he has no conflicts of interest.

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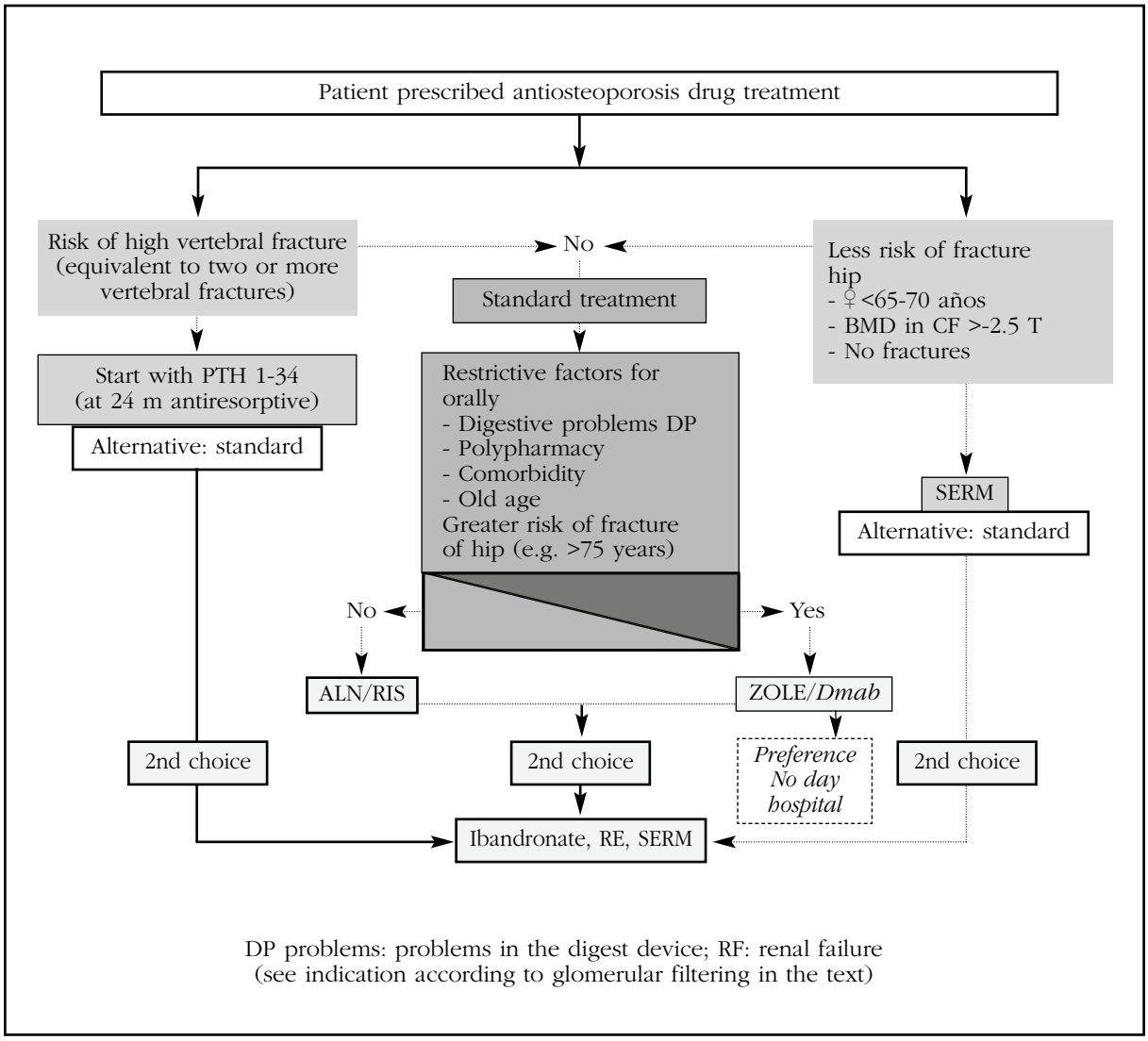
Figure 1. Treatment algorithm according to the 2014 SEIOMM GPC



DP problems: problems in the digest device; RF: renal failure
(see indication according to glomerular filtering in the text)

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SELF-ASSESSMENT TEST

1. How should the drafting of each of the recommendations of a CPG be?
   a. As long as you can follow the PICO format
   b. From 3 to 5 lines
   c. Concise, clear and easy to transfer to clinical practice
   d. A and C are correct

2. A recommendation that includes a meta-analysis or a systematic review corresponds to a grade of recommendation
   a. A
   b. B
   c. C
   d. D

3. Which of the following attributes according to the GPC is false with respect to alendronate
   a. It's economic
   b. It is well tolerated
   c. It is effective in both primary and secondary prevention of vertebral fracture
   d. It is a useful cost in the short and medium term, although not in the long term, in preventing hip fracture in women over 64 years of age

Answer key on page 24

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Treatment of osteoporosis

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Introduction

Fracture fractures are the only clinical complication of osteoporosis[1-3]. Therefore, treatment should be aimed at preventing the appearance of fractures, since they are associated with an increase in morbidity and mortality[4,5]. In this sense, the presence of fragility fractures is a cause for alarm and treatment needs to be established as early as possible. It is wrong to think that when we treat a fractured patient we have arrived late and that it is not cost-beneficial to start treatment, because, on the one hand, having suffered a fragility fracture is a risk factor for a new fracture and on the other hand, the establishment of treatment for osteoporosis not only reduces the risk of new fractures, but also decreases the mortality of patients who have suffered them[5,6].

The osteoporosis treatment pyramid

Figure 1 shows the "osteoporosis treatment pyramid"[7]. Treatment should commence by indicating a series of general non-pharmacological measures, summarized in table 1. These measures have been shown to be effective in reducing the risk of the appearance of fragility fractures[8,9]. From the moment osteoporosis is diagnosed, patients who smoke should be advised to stop smoking, and all those who carry out load-bearing physical exercise, according to their physical state (walking being the simplest and the first that should indicate), recommending to do it for 1 hour a day, which can be fractioned[8,10]. Patients who have appropriate physical condition can dance or practice activities in a gym, such as Tai-Chi[11] or Pilates[12] if they choose. Weight-lifting exercises should be avoided, especially those involving flexion of the spine due to the risk of vertebral fracture.

Patients are instructed to maintain a balanced, healthy diet, which must include dairy products[12]. Depending on weight and lipid metabolism, dairy products can be taken in skim or whole form, since the amount of calcium is the same, differing only in levels of fat. It is a mistake to restrict or eliminate dairy products from the diet, as it leads to the development of a negative balance in calcium metabolism and the production of secondary hyperparathyroidism, which worsens osteoporosis[12]. Before starting treatment with osteoporosis drugs, it is advisable that patients visit their dentist to check their mouth and resolve any pathology that may require further surgical manipulation: extractions, de-vitalizations, implants, etc. Thus, one of the most important risk factors in the appearance of maxillary osteonecrosis (ONJ), may be eliminated[13,14].

Most fragility fractures occur as a result of a fall and, therefore, it is advisable at the time of gaining clinical history data, to ascertain whether patients are suffering from repeated falls and to find out the possible causes[15], to act on them as much as

Figure 1. Osteoporosis treatment pyramid

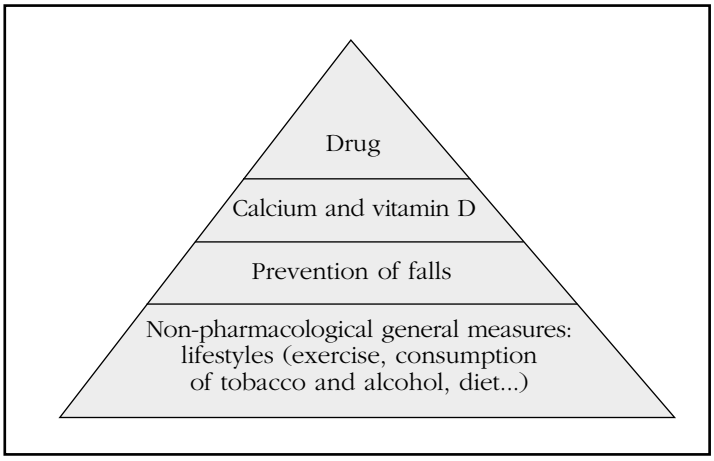

Table 1. Risk factors to be taken into account in the treatment of osteoporosis and its possible solution

Risk factor	Possible solution
Sedentary	Performing exercise daily. Walking
Tobacco	Give up smoking
Consumption of alcohol	Moderate consumption
Polypharmacy	Review your need and stop any drug that is not essential
Unbalanced diet	Healthy diet with dairy
Mouth in poor condition	Visit the dentist

possible. In this sense it should be taken into account that most of the falls are usually produced inside the house and, in it, in the bathroom. Polypharmacy, so prevalent among the elderly, must also be monitored and, on occasion, it can condition an increased risk of falls[16].

Is it necessary to administer calcium and vitamin D?

Yes, for several reasons. First and foremost, because all the reference studies conducted to establish the risk reduction of fragility fractures have been carried out by administering a supplement of calcium and vitamin D[7] to the patients. If we want to obtain the same results for which the drug was approved for use in patients, we should, if possible, try to reproduce the same clinical conditions as in the study. Second, most patients with osteoporosis and fragility fractures have hypovitaminosis D and do not ingest the recommended amounts of calcium by consensus[17]. Finally, although controversial, calcium and vitamin D supplementation may have a certain beneficial effect in reducing the risk of new fractures, especially in the hip and in patients with previous hypovitaminosis[14-17]. without forgetting that vitamin D supplements have been shown to be effective in reducing the risk of falls[15,16]. For all these reasons, it is advisable to administer 1,000 IU/day of vitamin D3 and 600 mg/day of calcium to all patients under treatment for osteoporosis[18-20].

Which drug to choose? Are they all the same?

The drug should be chosen according to the circumstances of each patient, once we have made the complete clinical assessment and diagnosed osteoporosis[1,7,21,22]. In principle, we should use a drug that reduces the risk of suffering any fracture: vertebral, non-vertebral and hip, but at this time in the vademecum of our country we have only 4 drugs that meet this requirement: alendronate, risedronate, zoledronate, and denosumab[7,22]. Strontium ranelate has recently been withdrawn from the market as well as calcitonin and other bisphosphonates (etidronate, pamidronate and ibandronate), selective modulators of estrogen receptors (SERMs) and the two parathormones (teriparatide and intact PTH) which do not reduce the risk of fracture of the femur (Table 2).

As indicated in another study of this collection, there is agreement in practically all the national and international therapeutic guidelines to consider alendronate and risedronate as the primary drugs of choice in osteoporosis treatment[7,22-26].

Although it reduces the risk of all fragility fractures, zoledronate is administered iv and its use is reserved for the hospital setting, which is why it is considered a second-choice drug[7,22]. Denosumab must also be administered by injection, subcutaneously, and is also considered a second-choice drug[22,26].

Teriparatide and, within SERMs, bazedoxifene are drugs to be taken into account in certain circumstances. Thus, if the patient presents vertebral fractures at the time of diagnosis or presents very low BMD levels, two-year treatment with teriparatide could begin, which is allowed by the health authorities[26]. Once finished, another drug should be continued. It has been reported that after suspending teriparatide, the addition of a bisphosphonate prolonged the beneficial effect in reducing the risk of fracture[29] although there is a certain residual effect[28].

Bazedoxifene can be used as an alternative to alendronate and risedronate, when these cannot be used for any reason[7,22,26], but its clinical spectrum is totally opposite to teriparatide, since it would be indicated in patients with a lower risk of hip fracture[26].

Denosumab is a potent antiresorptive that completely reduces fragility fracture risk[30]. In all therapeutic guidelines, it is considered a second-line drug and alternative to alendronate and risedronate[7,21-26,31,32]. On the one hand, it is to be administered parenterally every other year. On the other hand, at its price that almost triples the annual cost of alendronate[27] and, finally, because several articles have recently been published that show that, if patients are not strictly compliant, or if the drug is discontinued, there may be a notable loss of previously obtained BMD and an alarming increase in the incidence of new vertebral fractures[33,34]. This may already be observed 6

months after suspending the drug, which in clinical practice is equivalent to forgetting a dose.

In a recent meta-analysis, it was concluded that the best initial treatment for postmenopausal osteoporosis, in terms of cost-effectiveness, is alendronate or zoledronate, both generic[31].

How long should treatment with a drug be maintained?

The so-called therapeutic holidays

Most studies conducted to assess the efficacy and safety of drugs used in the treatment of osteoporosis have been designed with a follow-up of 3 years. Exceptionally, five-year follow-ups have been carried out with calcitonin and strontium ranelate (remarkably, both drugs have been withdrawn from the pharmaceutical market because of their side effects). We have observational data after a few years follow-up of the cohorts of the original studies on alendronate and risedronate, and six-year data with zoledronate[35]. The best long-term data collected are those obtained by the study conducted with denosumab, which lasted up to 10 years.

All of them have shown that the beneficial effect on the reduction of the risk of fracture is maintained during this time, and that in the case of some bisphosphonates there is a beneficial "residual" effect that is maintained even after the drug has been suspended, specifically for alendronate, risedronate and zoledronate[35].

In recent years, a current of opinion has developed which suggests that, in patients treated with bisphosphonates over a certain number of years, suspension should be considered to avoid two possible complications. These are osteonecrosis of the maxillary and atypical fractures or diaphyseal fractures[21,35-37]. This conclusion has been shared and recommended by several major scientific societies, because in these patients, studying the clinical factors associated with the appearance of these complications, bisphosphonate use for more than five years could be one of the causes[22,35-40].

It is a controversial issue, with discrepancies[41]. We believe that the so-called therapeutic holidays, (simply suspending treatment), are indicated to patients who tolerate the drug well, which is being effective in reducing the risk of fracture and that has not produced any side effects and has forced its withdrawal. Bisphosphonate is suspended on a preventive basis in these patients before possible complications, which have not yet occurred. The risk of these complications is very low, clearly lower than the risk that patients have of suffering a fragility fracture for which the drug was indicated. Therefore, our opinion is that as long as the patient tolerate the treatment well and no reasons have been identified to suspend the drug due to side effects or intolerance, it should be continued as long as possible[40]. In addition, as the years of treatment with the drug go by, the patient increases in age, which is one of the main risk factors for fragility fracture.

Conclusion

The treatment of osteoporosis should be directed mainly at the secondary prevention of fractures. The appearance of adverse effects related to drugs

Table 2. Degree of anti-fracture efficacy of drugs used in the treatment of osteoporosis (according to the recommendation grades of the Oxford Center for Evidence-Based Medicine)

Drug	Fracture vertebral	Fracture no vertebral	Hip fracture	Others
Alendronate	A	A	A	
Risedronate	A	A	A	
Etidronate	A	No	No	It has no indication
Ibandronate	A	B*	No	
Zoledronate	A	A	A	
Denosumab	A	A	A	
Raloxifene	A	No	No	
Bazedoxifene	A	B*	No	
Teriparatide	A	A	No	
PTH 1-84	A	No	No	Abandoned
Calcitonin	A	No	No	Retired
Strontium	A	A	A	Retired
Estrogens	A	A	A	It has no indication

A: highest grade of recommendation, based on consistent randomized clinical trials.
B: second grade recommendation, based on cohort studies or consistent case studies and controls.
*In post hoc analysis of a subgroup of patients demonstrated anti-fracture efficacy.

for the osteoporosis treatment has made medical professionals re-evaluate the indications, the time of treatment and even withdraw the commercialization of some of them.

General non-pharmacological measures should be observed, the risk of falls assessed and calcium and vitamin D supplemented in all cases.

In general, antiresorptive drugs (alendronate and risedronate) are considered the first choice. Zoledronate or denosumab are second-line drugs and will be indicated in cases of digestive intolerance, poor adherence or an increased risk of hip fracture. Teriparatide will be indicated in patients with 2 or more previous vertebral fractures or with very low bone density.

Conflict of interests: The authors declare no conflict of interests.

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SELF-ASSESSMENT TEST

1. One of the following drugs has recently been considered in a meta-analysis as of first choice, with the best cost-effectiveness balance. The correct answer is:
    a. Alendronate
    b. Ibandronate
    c. Risedronate
    d. Denosumab

2. One of the following measures is not part of the "base" of the osteoporosis treatment pyramid. The correct answer is:
    a. Exercise adequate fitness
    b. Follow a healthy balanced diet
    c. Stop smoking
    e. Administer calcium and vitamin D

3. One of these drugs does not reduce hip fracture risk:
    a. Denosumab
    b. Alendronate
    c. Ibandronate
    d. Risedronate

Answer key on page 24

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Adherence as a problem in osteoporosis: Alendronate soluble as a solution

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Introduction

The decision regarding pharmacological treatment of osteoporosis should be based on three fundamental pillars: the proven anti-fracture effectiveness of the chosen drug, its safety that will condition patient tolerability and the adherence that ensures the therapy is maintained as long as necessary, presumably from the time of diagnosis.

Osteoporosis (OP) as a chronic disorder with a relatively long initial course and asymptomatic to its complications represents a major problem of individual health and public health due to the costs involved. In addition, the therapeutic regimens currently available are uncomfortable and, therefore, contribute to the patient's low therapeutic adherence[1]. Adherence is defined as compliance with the exact prescription provided to the patient and extended over the time indicated. When treating a chronic disorder, nothing can be achieved in the long term without persistence. Factors that influence treatment adherence include the prescribing physician's explanations, the characteristics of the disease and the patient's attitudes, but also the therapeutic regimen.

Other authors have indicated that the factors that influence OP therapy adherence include the cost of medications, adverse effects, frequency of dosage, education about the disease, patient follow-up and participation in the treatment decisions[2,3]. As maintaining treatment adherence is fundamental, extensive follow-up studies report (9,851 postmenopausal women referred to 141 Italian centers for OP management) that, in general, 19.1% of patients discontinued the prescribed medication before attending re-evaluations of bone mass, more than half of them in the first 6 months. The interruption rate was significantly different among treatments. The most frequent reasons for interruption were side effects related to medications, insufficient motivation for treatment and fear of these side effects[3]. The best medication is ineffective if it is not taken as it should be and the benefits of the treatment are lost if the patient does not take the medication. We currently know that patients with gastrointestinal symptoms have less adherence to treatment and worse quality of life in relation to health than patients without gastrointestinal symptoms[4].

OP treatment should be maintained. Non-adherent patients experience more limited decreases in bone resorption levels and worse bone mass results as well[5]. A recent meta-analysis (which included 236,540 patients) showed that adherence is finally necessary for the maintenance of anti-fracture efficacy with a 46% increase in fracture risk in non-adherent patients[6]. It has been observed that adhesions below 80% correlate with significant decreases in protection against fractures. Thus, when the adhesion is between 80 and 90%, the risk of fractures increases by 9%, but if it is between 50 and 80%, the risk increases by 18% and up to 21% when the adherence drops. beyond 50%[7], according to data from the monitoring of a database of 38,120 women with OP with a mean age of 66 years and a mean follow-up of 1.7 years. This probably has a considerable impact on the quality of life and healthcare costs, since the improvement of compliance in real practice can significantly reduce the risk of OP-related fracture[8].

Improvement of adherence as a therapeutic objective in OP

Much scientific evidence indicates that an adequate efficacy of the different treatments against OP has been achieved, improving adherence is one of the basic objectives to improve the long-term

expectation of the disease[9] and reduce the rate of fractures, a primary objective of any treatment[1,2]. It has also been shown that better adherence facilitates a better cost-effectiveness balance of OP[10] drug treatment at a time in our history when efficiency is increasingly valued, sometimes even more than efficacy itself.

Bisphosphonates (BFs) are drugs of first choice in OP according to multidisciplinary clinical practice guidelines[11]. Surely, among all of them, alendronate (ALN) as paradigmatic, because it is probably the one with the most clinical research available. However, the frequent gastrointestinal side effects of the group tend to be a reason to abandon treatment in a high percentage of cases[12]. In fact, prescribers perceive it when they highlight in well-designed surveys a low therapeutic adherence, mainly associated with side effects, polypharmacy and lack of communication between professionals[13]. In this same study it is pointed out that the restriction of eating and drinking before and after the taking of the drug is the administration instruction more difficult to follow by the patients and stands out as basic to increase the safety of the drug, which may be contradictory. In this order of things, new formulations that improve the digestive tolerance of ALN seem a good contribution to improve the adherence of a first-line drug[12].

Improved safety by making alendronate soluble

The basic aim should be to reduce gastrointestinal side effects in the general framework of improving both patient compliance and therapeutic persistence, since most of the treatment discontinuations related to secondary diseases are due to gastrointestinal problems. A microencapsulation of alendronate sodium was initially designed to reduce mucous damage in rats, with polymeric microparticles as a promising way to administer ALN orally[12,14]. Immediately afterwards this formula was produced as water soluble to facilitate intake even more[14-16] and thus reduce the possible impact that a rather large tablet could have on contact with the digestive mucosa. This would eliminate, among other factors, the enormous variability that the disintegration of tablets could have in facilitating their absorption, which had been shown to be of paramount importance in previous studies[17]. In fact, some ALN tablets only dissolved 80% after 20 minutes, taking up to 30 minutes to dissolve about 88%. In this study, differences in the disintegration and subsequent dissolution of the tablets were found to reduce bioavailability and effectiveness in relation to what was expected by the original drug. In fact, longer or shorter disintegration times may increase the risk of esophagitis due to ALN. The soluble formulation could represent an accessory solution that would improve this aspect[15,16].

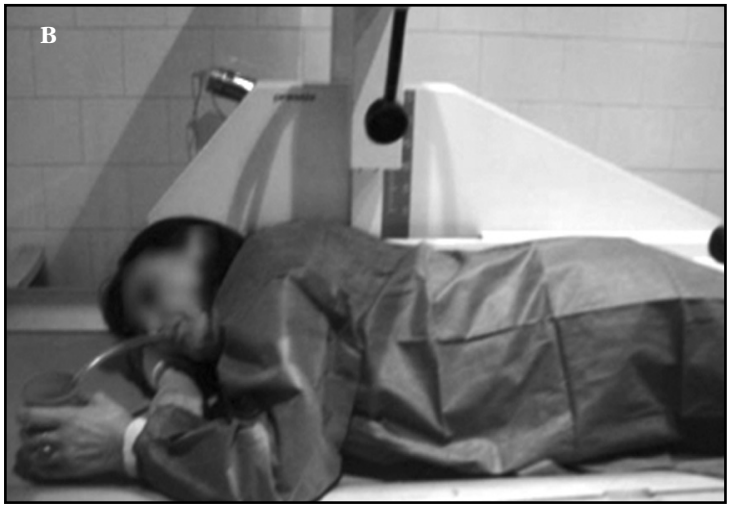
The first description of an oral drinking solution of ALN is more than 14 years old. Each bottle contained 70 mg of ALN, with citrate as a buffer, with an artificial raspberry flavor, parabens as preservatives and saccharin as a sweetener. With this formulation, more extra water (drinkable ALN was bioequivalent to 70 mg tablets), a 6-month placebo-controlled clinical study was conducted that treated 392 postmenopausal women. Adverse events were generally mild to moderate and did not result in treatment interruption, with most patients considering the taste of the drink that could be acceptable[18]. Subsequently, different formulas of soluble ALN were developed and tested, all of them bio-equivalents. The results showed that the drinkable ALN was a bioequivalent formulation to the tablets in terms of absorbed ALN (they were within the acceptance limits of between 80 and 125%) and may be advantageous in patients in which the transit or disintegration of the tablets were not adequately attained[15].

In a subsequent prospective clinical study, the rhythm of gastric emptying was evaluated with scintigraph study by labeling with 99mTc-DTPA and pH using direct nasogastric tubes, after administering "conventional" ALN tablets and effervescent form with a buffer to improve safety. Neither form affected the esophagus and there were no relevant or statistically significant differences in gastric emptying. The mean pH measured at the time of 50% gastric emptying of the radiolabel was significantly higher in the subjects treated with effervescent formulation compared with those treated with the tablets[18]. The new ALN form was found to reduce the exposure of the gastric mucosa to a pH level <3, which per se represents a risk factor for irritation of the gastro-esophageal mucosa[12,19].

In 2013, a soluble ALN product with 70 mg weekly (called bonasol in Austria, Belgium, Czech Republic, Denmark, Finland, France, Greece, Hungary, Ireland, Italy, the Netherlands) was approved in decentralized countries by decentralized procedure. Norway, Portugal, Romania, Slovak Republic and with other trade names in Sweden, Germany and the United Kingdom, as well as in Spain - soludronate), whose objective is to provide a friendlier way with ALN patients, which will lead to greater compliance and with a cost similar to that of generic ALN tablets[15,20,21].

This new water-soluble form has potential advantages since it avoids the adhesion of the conventional tablet to the gastric mucosa, also overcoming all the motility obstacles (for example, those present in the hernia, the spasms, the position of the patient's body during the transit) and thus eliminating the variability in the tablet's disintegration rate with the consecutive irritation by reflux of particles and control of the pH of the gastric fluid[20]. The bio-equivalence of this drinking solution of ALN 70 mg in 100 ml was compared and confirmed by means of a randomized controlled study against reference tablets in 104 healthy volunteers. The transit time was also compared according to 24 male and female healthy volunteers (average age 52 years) standing or lying prone on the right side during the intake of the product, by means of a video recording of the swallowing

Figure 1. Position of the body of the participants during the study (reference[20]) of transit of the upper digestive tract. A. Left foot position. B. Resting position in bed in prone right decubitus position



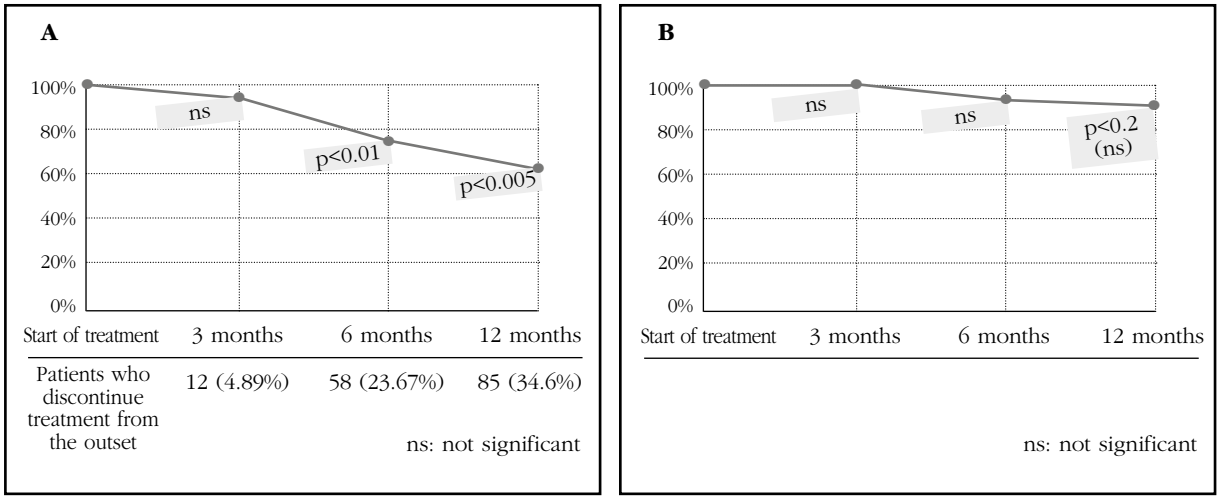
with X-rays, to characterize the esophageal passage time of the two ALN formulations. When taken in the standing position (Figure 1A), both formulations had equal mean transit times from mouth to stomach, but the dispersion was significantly less with the liquid form. When taken lying down (Figure 1B), the drinkable ALN had shorter and less variable average transit times compared to conventional tablets. These results show that soluble and drinkable ALN is bioequivalent to the tablets and can be advantageous in patients with delayed transit or in whom the disintegration of the tablets causes some damage[20].

Different clinical trials of casuistry collection[4,6,9,16] report clinical adherence of 34.5% (with n of 245 patients) (Figure 2A) and up to 60% for the first year of treatment with BFs, specifically with ALN. A prospective follow-up study[16] finally showed with 118 patients who took soluble ALN, that none had discontinued the therapy after 3 months from the start of their treatment; after 6 months, 6 patients (5.08%) had discontinued their therapy (p=n.s). After 12 months, the therapy was suspended for 9 subjects (7.63% of the initial number). Therefore, 109 subjects were still receiving therapy (92.37% of the total they started) (p<0.2=n.s) (Figure 2B). Finally, the goal of significant improvement in adherence was achieved.

Conclusions

- ALN is a drug of first choice in the management of osteoporosis[11,22].
- A high percentage of patients abandon the treatments in their first year of therapy[1-3].
- Most treatment withdrawals are related to gastrointestinal problems and the recommended posology[4,13].
- The poor adherence of patients to treatments suggests identifying new alternatives to improve that[7-9].
- New formulations of effervescent or soluble ALN have shown better safety indices[12,14,15].
- Soluble and drinkable ALN reduces gastrointestinal side effects and is shown as a valid alternative to improve adherence[15,20].
- Soluble ALN has been shown to be prospectively effective in increasing adherence at one year, from 34.5% with conventional tablets up to 92.37%[16].

Figure 2. A. Patients (n=245) who discontinue treatment with ALN in "conventional" tablets during one year of treatment; 34.5% remain (modification of reference[16]). B. Patients (n=118) who discontinue treatment with ALN in drinkable solution during one year of treatment; 92.37% remain (idem reference)



Conflict of interests: The authors declare no conflict of interests.

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SELF-ASSESSMENT TEST

1. Maintaining the right time a treatment is fundamental in any disease chronicle. The factors that influence the adherence to the treatment of osteoporosis, they are at your discretion:
   a. The explanations of the prescribing doctor
   b. The characteristics of the disease
   c. The patient's attitudes, but also the therapeutic regimen applied
   d. All of the above

2. Adherence to a certain treatment in a chronic disease such as osteoporosis can be improved by the following different strategies, except one:
   a. Order the treatment with explanations even in writing and severely penalize the breach
   b. Facilitate the dosage of the drug with more friendly guidelines
   c. Improve safety in the gastrointestinal area
   d. Inform the patient of the increase in the fracture rate among people who they abandon their treatments

3. The new formulations of ALN, both effervescent and soluble drinkable have demonstrated all of the following statements, except one:
   a. Favor a reduction of secondary gastrointestinal origin
   b. Improve adherence significantly up to 92% in the first year of treatment
   c. Implement the solution of all the complications of osteoarthritis, I'm afraid
   d. Increase the safety of the drug to encourage therapeutic compliance

Answer key on page 24

SELF-ASSESSMENT TEST *(answer key)*

Osteoporosis: Concept. Pathophysiology Clinic. Epidemiology

1. Which of the following statements is not true?
   c. The osteocyte regulates RANKL synthesis
2. Which of the osteoporotic fractures (fx) is the most frequent in clinical practice?
   a. vertebral fx
3. Which of the following statements is not true?
   c. Mortality after a hip fx is less than 10%

Osteoporosis and Primary Care. How to assess the risk of fracture. Use of the risk scales

1. Which of these is not considered a major risk factor for fracture?
   b. BMI 20.5 Kg/m²
2. Which of these scales allows the estimation of the risk of fracture of the femur at 5 years?
   d. B and C
3. According to the Spanish calibration of FRAX© of Azagra, indicate the correct one:
   b. A risk of major fracture without BMD of 10% recommends assessing treatment

Clinical practice guidelines on osteoporosis

1. How should the drafting of each of the recommendations of a CPG be?
   c. Concise, clear and easy to transfer to clinical practice
2. A recommendation that includes a meta-analysis or a systematic review corresponds to a grade of recommendation
   a. A
3. Which of the following attributes according to the GPC is false with respect to alendronate
   d. It is useful cost in the short and medium term, although not in the long term, in the prevention of hip fracture in women over 64 years of age

Treatment of osteoporosis

1. One of the following drugs has recently been considered in a meta-analysis as of first choice, being the one with the best cost-effectiveness balance. Is about:
   a. Alendronate
2. One of the following measures is not part of the "base" of the pyramid in the treatment of osteoporosis. Is about:
   e. Administer calcium and vitamin D
3. One of these drugs does not reduce the risk of hip fracture:
   c. Ibandronate

Adherence as a problem in osteoporosis: Alendronate soluble as a solution

1. Maintaining the right treatment is fundamental in any chronic disease. The factors that influence treatment adherence in osteoporosis are:
   d. All of the above
2. Adherence to a certain treatment in a chronic disease such as osteoporosis can be improved by the following different strategies, except one:
   a. Order the treatment with explanations even in writing and penalize severely non-compliance
3. The new formulations of ALN, both effervescent and soluble drinkable have demonstrated all of the following statements, except one:
   c. Implement the solution of all the complications of osteoarthritis, I'm afraid

1 NOMBRE DEL MEDICAMENTO. Soludronate Semanal 70 mg solución oral **2. COMPOSICIÓN CUALITATIVA Y CUANTITATIVA.** Cada dosis única de 100 ml contiene 70 mg de ácido alendrónico (como 91,35 mg de alendronato sódico trihidrato). Excipientes: Cada dosis (100 ml) contiene 80 mg de parahidroxibenzoato de metilo (E218), 20 mg de parahidroxibenzoato de propilo (E216) y 6 mg de amarillo anaranjado (E110). Para consultar la lista completa de excipientes, ver sección 6.1. **3. FORMA FARMACÉUTICA.** Solución oral. Solución opalescente de color naranja. **4. DATOS CLÍNICOS. 4.1 Indicaciones terapéuticas.** Tratamiento de la osteoporosis posmenopáusica. El ácido alendrónico reduce el riesgo de fracturas vertebrales y de cadera. **4.2. Posología y forma de administración.** Posología. Para administración oral. La posología recomendada es una dosis unitaria de 70 mg (100 ml) una vez a la semana. No se ha establecido la duración óptima del tratamiento con bisfosfonatos para la osteoporosis. La necesidad de continuar con el tratamiento debe ser reevaluada periódicamente considerando los beneficios y riesgos potenciales de Soludronate Semanal para cada paciente de forma individualizada, sobre todo tras 5 o más años de uso. Método de administración. • *Para permitir una absorción adecuada del ácido alendrónico* Soludronate Semanal se debe tomar al menos 30 minutos antes de la primera comida, bebida o medicamento del día sólo con agua corriente. Es probable que otras bebidas (como el agua mineral), alimentos y algunos medicamentos disminuyan la absorción del ácido alendrónico (ver sección 4.5). • *Para facilitar la liberación en el estómago y, en consecuencia, disminuir la posibilidad de irritación local y esofágica/acontecimientos adversos (ver sección 4.4).* Las pacientes no deben tumbarse hasta después de su primera comida del día, que debe realizarse al menos 30 minutos después de tomar la solución. Las pacientes no deben tumbarse durante al menos 30 minutos después de tomar Soludronate Semanal. Soludronate Semanal sólo debe ingerirse al levantarse por la mañana como una dosis única de 100 ml (todo el contenido del frasco) seguida de al menos 30 ml de agua corriente. Se puede tomar más agua (corriente). Soludronate Semanal no debe tomarse a la hora de acostarse o antes de levantarse por la mañana. Las pacientes deben recibir suplementos de calcio y vitamina D si el aporte con la dieta es insuficiente (ver sección 4.4). • *Uso en mujeres de edad avanzada:* En estudios clínicos no hubo diferencias relacionadas con la edad en los perfiles de eficacia o seguridad del ácido alendrónico. Por tanto, no es necesario ajustar la dosis en las mujeres de edad avanzada. • *Uso en la insuficiencia renal:* No es necesario ajustar la dosis en las pacientes con una filtración glomerular (FG) superior a 35 ml/min. No se recomienda administrar ácido alendrónico a las pacientes con insuficiencia renal y una FG inferior a 35 ml/min por la falta de experiencia. • *Uso en niños y adolescentes:* No se recomienda el uso de ácido alendrónico en niños menores de 18 años debido a que no existen datos suficientes en cuanto a su seguridad y eficacia en enfermedades asociadas con osteoporosis pediátrica (ver también sección 5.1). El ácido alendrónico no se ha investigado en el tratamiento de la osteoporosis inducida por glucocorticoides. **4.3 Contraindicaciones.** Anomalías del esófago y otros factores que retrasan el vaciamiento esofágico, como estenosis o acalasia. Incapacidad para permanecer de pie o sentada erguida durante al menos 30 minutos. Hipersensibilidad al ácido alendrónico o a cualquiera de los excipientes. Hipocalcemia. Pacientes con dificultad para tragar líquidos. Pacientes con riesgo de aspiración. Ver también 4.4 "Advertencias y precauciones especiales de empleo". **4.4 Advertencias y precauciones especiales de empleo.** Reacciones adversas del tracto gastrointestinal superior. Soludronate Semanal puede producir una irritación local de la mucosa gastrointestinal alta. Como existe la posibilidad de empeoramiento de la enfermedad subyacente, hay que administrar con precaución Soludronate Semanal a pacientes con problemas gastrointestinales altos activos, como disfagia, enfermedad esofágica, gastritis, duodenitis, úlceras o antecedente reciente (en el año anterior) de enfermedad gastrointestinal importante, como úlcera péptica o hemorragia gastrointestinal activa o cirugía de la porción superior del tubo digestivo distinta de la piloroplastia (ver sección 4.3). En las pacientes con esófago de Barrett confirmado, los médicos deben considerar de manera individual los beneficios y posibles riesgos de alendronato. Se han comunicado reacciones esofágicas (a veces graves y con necesidad de hospitalización), como esofagitis, úlceras esofágicas y erosiones esofágicas, rara vez seguidas de estenosis esofágica, en pacientes tratadas con ácido alendrónico. Por tanto, los médicos deben vigilar la aparición de signos o síntomas que indiquen una posible reacción esofágica, y debe decirse a las pacientes que suspendan el ácido alendrónico y acudan al médico si presentan síntomas de irritación esofágica, como disfagia, dolor al tragar o dolor retroesternal y aparición o empeoramiento de la pirosis. El riesgo de acontecimientos adversos esofágicos graves parece ser mayor en las pacientes que no toman el ácido alendrónico correctamente o que lo continúan tomando después de presentar síntomas indicativos de irritación esofágica. Es muy importante que la paciente reciba y comprenda las instrucciones posológicas completas (ver 4.2 "Posología y forma de administración"). Se debe informar a las pacientes de que el incumplimiento de estas instrucciones puede aumentar su riesgo de problemas esofágicos. Aunque no se ha observado un aumento del riesgo en ensayos clínicos extensos, ha habido casos raros (poscomercialización) de úlceras gástricas y duodenales, algunas graves y con complicaciones. Osteonecrosis de la mandíbula. Se ha descrito osteonecrosis de la mandíbula, generalmente asociada a extracción dental o infección local (como la osteomielitis), en pacientes con cáncer que recibían pautas de tratamiento que incluían primordialmente bisfosfonatos administrados por vía intravenosa. Muchas de estas pacientes también estaban recibiendo quimioterapia y corticosteroides. También se ha notificado osteonecrosis de la mandíbula en pacientes con osteoporosis tratadas con bisfosfonatos orales. Se deben tener en cuenta los siguientes factores de riesgo cuando se evalúe el riesgo individual de desarrollar osteonecrosis de la mandíbula: potencia del bisfosfonato (máxima para ácido zoledrónico), vía de administración (ver arriba) y dosis acumulada; cáncer, quimioterapia, radioterapia, corticosteroides, fumar; antecedentes de enfermedad dental, higiene bucal deficiente, enfermedad periodontal, procesos dentales invasivos y dentaduras postizas deficientemente ajustadas. Debe considerarse la realización de una exploración dental con tratamiento odontológico preventivo adecuado antes del tratamiento con bisfosfonatos en las pacientes con una situación dental deficiente. Mientras estén en tratamiento, estas pacientes deben evitar, si es posible, los procedimientos dentales invasivos. En las pacientes que experimenten osteonecrosis de la mandíbula mientras reciben bisfosfonatos, la cirugía dental puede agravar el proceso. En lo que respecta a las pacientes que requieren procedimientos dentales, no se dispone de datos que indiquen si la suspensión del tratamiento con bisfosfonatos reduce el riesgo de osteonecrosis de la mandíbula. El juicio clínico del médico responsable del tratamiento debe orientar el plan terapéutico de cada paciente basándose en una evaluación individual del beneficio-riesgo.Durante el tratamiento con bisfosfonatos, se debe animar a todas las pacientes a que mantengan una buena higiene oral, a que reciban revisiones dentales rutinarias y a que comuniquen cualquier síntoma oral, como movilidad dental, dolor o inflamación. Osteonecrosis del conducto auditivo externo. Se han notificado casos de osteonecrosis del conducto auditivo externo con el uso de bisfosfonatos, principalmente asociado con tratamientos de larga duración. Los posibles factores de riesgo de osteonecrosis del conducto auditivo externo incluyen el uso de esteroides y la quimioterapia; existen también factores de riesgo locales como infección o traumatismo. Debe tenerse en cuenta la posibilidad de osteonecrosis del conducto auditivo externo en pacientes que reciben bisfosfonatos y presentan síntomas auditivos como infecciones de oído crónicas. Dolor musculoesquelético. Se ha observado dolor óseo, articular o muscular en pacientes tratadas con bisfosfonatos. En la experiencia poscomercialización, estos síntomas rara vez han sido intensos o incapacitantes (ver sección 4.8). El intervalo hasta el inicio de los síntomas varió entre un día y varios meses después de empezar el tratamiento. En la mayoría de los casos, los síntomas disminuyeron después de suspender la medicación. En un subgrupo los síntomas reaparecieron al volver a administrar el mismo medicamento u otro bisfosfonato. Fracturas atípicas de fémur. Se han notificado casos de fracturas atípicas subtrocantéricas y diafisarias del fémur asociadas al tratamiento con bisfosfonatos, principalmente en pacientes en tratamiento prolongado para la osteoporosis. Estas fracturas transversales u oblicuas cortas pueden ocurrir en cualquier parte a lo largo del fémur, desde justo debajo del trocánter menor hasta justo por encima de la cresta supracondílea. Estas fracturas se producen después de un traumatismo mínimo o en ausencia de él y algunos pacientes tienen dolor en el muslo o en la ingle, a menudo asociado con imágenes características de fracturas por sobrecarga, semanas a meses antes de que se presente la fractura femoral completa. Las fracturas son generalmente bilaterales; por lo tanto, el fémur del lado opuesto debe ser examinado en los pacientes tratados con bisfosfonatos que hayan tenido una fractura de la diáfisis femoral. También se ha notificado un bajo índice de consolidación de estas fracturas. Debe considerarse la interrupción del tratamiento con bisfosfonatos, valorando de forma individualizada el balance beneficio/riesgo, en aquellos pacientes en los que exista sospecha de fractura atípica de fémur pendiente de evaluación. Durante el tratamiento con bisfosfonatos debe advertirse a los pacientes que notifiquen cualquier dolor en el muslo, cadera o ingle. En cualquier paciente que presente dichos síntomas deberá valorarse si existe una fractura de fémur incompleta. Reacciones en la piel. Durante la experiencia post-comercialización, se han notificado casos raros de reacciones cutáneas graves incluyendo síndrome de Stevens-Johnson y necrólisis epidérmica tóxica. Olvido de una dosis. Hay que indicar a las pacientes que si omiten la dosis de *ácido alendrónico 70 mg solución oral,* deben tomar una sola dosis unitaria (100 ml) a la mañana siguiente de recordarlo. No deben tomar otras dosis el mismo día, pero deben volver a tomar una dosis unitaria una vez a la semana, el mismo día originalmente programado. Insuficiencia renal. No se recomienda administrar ácido alendrónico a las pacientes con insuficiencia renal y FG inferior a 35 ml/min (ver sección 4.2). Metabolismo óseo y mineral. Hay que considerar las causas de osteoporosis distintas de la carencia de estrógenos y el envejecimiento. Es necesario corregir la hipocalcemia antes de iniciar el tratamiento con ácido alendrónico (ver sección 4.3). También se deben tratar con eficacia otros trastornos que afecten al metabolismo mineral (como carencia de vitamina D e hipoparatiroidismo). En las pacientes con estos trastornos hay que vigilar el calcio sérico y los síntomas de hipocalcemia durante el tratamiento con Soludronate Semanal. A causa de los efectos positivos del ácido alendrónico en cuanto a aumento del mineral óseo, se pueden producir disminuciones de las concentraciones séricas de calcio y fosfato, en particular en pacientes que están tomando glucocorticoides en las que la absorción de calcio puede estar reducida. Tales disminuciones suelen ser ligeras y asintomáticas. Sin embargo, ha habido casos raros de hipocalcemia sintomática, ocasionalmente grave y a menudo en pacientes con trastornos predisponentes (p. ej., hipoparatiroidismo, carencia de vitamina D y malabsorción de calcio). Es particularmente importante garantizar un aporte suficiente de calcio y vitamina D en las pacientes tratadas con glucocorticoides. Excipientes Este medicamento contiene un volumen del 0,15% de etanol (alcohol), es decir, hasta 115 mg por dosis, lo que equivale a 3 ml de cerveza o 1,3 ml de vino por dosis, por lo que es perjudicial para las pacientes alcohólicas. Es necesario tener esto en cuenta en grupos de alto riesgo, como las pacientes con hepatopatía o epilepsia. Este medicamento puede producir reacciones alérgicas porqué contiene el colorante amarillo anaranjado (E-110). Puede provocar asma, especialmente en pacientes alérgicos al ácido acetilsalicílico. Este medicamento puede producir reacciones alérgicas (posiblemente retardadas) porqué contiene parahidroxibenzoato de metilo (E218) y parahidroxibenzoato de propilo (E216). **4.5 Interacción con otros medicamentos y otras formas de interacción.** Si se toman al mismo tiempo, es probable que los alimentos y bebidas (incluida el agua mineral), los suplementos de calcio, los antiácidos y algunos fármacos orales interfieran en la absorción del ácido alendrónico. Por ello, las pacientes deben esperar al menos 30 minutos después de tomar el ácido alendrónico antes de tomar cualquier otro medicamento (ver las secciones 4.2 y 5.2). No se prevén otras interacciones clínicamente importantes con medicamentos. En los ensayos clínicos, algunas pacientes recibieron estrógenos (por vía intravaginal, transdérmica u oral) durante la administración del ácido alendrónico. No se observaron acontecimientos adversos atribuibles a su uso concomitante. Como los AINE producen irritación gastrointestinal, es obligada la precaución durante el uso concomitante con alendronato. Aunque no se han realizado estudios de interacciones específicas, en los ensayos clínicos el ácido alendrónico se empleó de forma concomitante con una amplia variedad de fármacos de uso habitual sin indicios de interacciones adversas clínicas. **4.6 Fertilidad, embarazo y lactancia.** Embarazo. No hay datos o estos son limitados sobre el uso de alendronato en mujeres embarazadas. Los estudios con animales han mostrado toxicidad reproductiva. El ácido alendrónico administrado durante la gestación a ratas causó distocia relacionada con hipocalcemia (ver sección 5.3). Soludronate Semanal 70 mg solución oral no debe administrarse durante el embarazo. Lactancia. No se sabe si alendronato se excreta en la leche materna humana. El riesgo para los recién nacidos/infantes no puede ser descartado. El ácido alendrónico no se debe administrar a mujeres lactantes. Fertilidad. Los bifosfonatos se incorporan a la matriz ósea, desde la cual son liberados gradualmente durante años. La cantidad de bifosfonatos incorporados en los huesos de un adulto y, por lo tanto, la cantidad disponible para liberarse a la circulación sistémica se encuentra directamente relacionada con la posología y la durada del tratamiento (ver sección 5.2). No hay datos disponibles del riesgo fetal en humanos. Sin embargo, existe un riesgo teórico de daño fetal, predominantemente óseo, si una mujer que ha completado una pauta terapéutica con bifosfonatos se queda embarazada. El impacto de variables como el tiempo entre la suspensión del tratamiento con bifosfonatos y la concepción, el tipo de bifosfonato usado, y la ruta de administración (intravenoso frente a oral) en el riesgo fetal no ha sido estudiado. **4.7 Efectos sobre la capacidad para conducir y utilizar máquinas.** La influencia del ácido alendrónico sobre la capacidad para conducir y utilizar máquinas es nula o insignificante. No obstante, algunas reacciones adversas que se han notificado con el ácido alendrónico pueden afectar a la capacidad de algunas pacientes de conducir o usar maquinaria. Las respuestas individuales a Soludronate Semanal pueden variar (ver sección 4.8). **4.8 Reacciones adversas.** En un estudio de un año de mujeres posmenopáusicas con osteoporosis, los perfiles globales de seguridad del ácido alendrónico una vez a la semana en comprimidos (n = 519) y del ácido alendrónico 10 mg al día (n = 370) fueron similares. En dos estudios de tres años de diseño prácticamente idéntico, en mujeres posmenopáusicas (ácido alendrónico 10 mg: n = 196; placebo: n = 397), los perfiles globales de seguridad del ácido alendrónico 10 mg al día y del placebo fueron semejantes. A continuación, se presentan los acontecimientos adversos notificados por los investigadores como posiblemente, probablemente o claramente relacionados con la medicación en caso de producirse en ≥1% de cualquier grupo de tratamiento en el estudio de un año o en ≥1% de las pacientes tratadas con alendronato 10 mg/día y con una incidencia mayor que en las pacientes tratadas con el placebo en los estudios de tres años: Estudio de un año: ***a)*** *Ácido alendrónico una vez a la semana en comprimidos* (n = 519): • *Digestivos:* Dolor abdominal 3,7%, Dispepsia 2,7%, Regurgitación de ácido 1,9%, Náuseas 1,9%, Distensión abdominal 1,0%, Estreñimiento 0,8%, Diarrea 0,6%, Disfagia 0,4%, Flatulencia 0,4%, Gastritis 0,2%, Úlcera gástrica 0,0%, Úlcera esofágica 0,0%. • *Osteomusculares:* Dolor osteomuscular (dolor óseo, muscular o articular) 2,9%, Calambres musculares 0,2%. • *Neurológicos:* Cefalea 0,4%. ***b)*** *Ácido alendrónico 10 mg al día (n=370):* • *Digestivos:* Dolor abdominal 3,0%, Dispepsia 2,2%, Regurgitación de ácido 2,4%, Náuseas 2,4%, Distensión abdominal 1,4%, Estreñimiento 1,6%, Diarrea 0,5%, Disfagia 0,5%, Flatulencia 1,6%, Gastritis 1,1%, Úlcera gástrica 1,1%, Úlcera esofágica 0,0%. • *Osteomusculares:* Dolor osteomuscular (dolor óseo, muscular o articular) 3,2%, Calambres musculares 1,1%. • *Neurológicos:* Cefalea 0,3%. Estudio a tres años: ***a)*** *Ácido alendrónico 10 mg al día (n=196)* • *Digestivos:* Dolor abdominal 6,6%, Dispepsia 3,6%, Regurgitación de ácido 2,0%, Náuseas 3,6%, Distensión abdominal 1,0%, Estreñimiento 3,1%, Diarrea 3,1%, Disfagia 1,0%, Flatulencia 2,6%, Gastritis 0,5%, Úlcera gástrica 0,0%, Úlcera esofágica 1,5%. • *Osteomusculares:* Dolor osteomuscular (dolor óseo, muscular o articular) 4,1%, Calambres musculares 0,0%. • *Neurológicos:* Cefalea 2,6%. ***b)*** *Placebo (n=397)* • *Digestivos:* Dolor abdominal 4,8%, Dispepsia 3,5%, Regurgitación de ácido 4,3%, Náuseas 4,0%, Distensión abdominal 0,8%, Estreñimiento 1,8%, Diarrea 1,8%, Disfagia 0,0%, Flatulencia 0,5%, Gastritis 1,3%, Úlcera gástrica 0,0%, Úlcera esofágica 0,0%. • *Osteomusculares:* Dolor osteomuscular (dolor óseo, muscular o articular) 2,5%, Calambres musculares 1,0%. • *Neurológicos:* Cefalea 1,5%. También se han notificado los siguientes efectos adversos durante los estudios clínicos o el uso poscomercialización: Las frecuencias se definen como: Muy frecuentes (≥1/10), frecuentes (≥ 1/100, < 1/10), poco frecuentes (≥ 1/1000, < 1/100), raros (≥ 1/10.000, < 1/1000), muy raros (< 1/10.000 incluidos los casos aislados) Trastornos del sistema inmunitario: *Raros*: reacciones de hipersensibilidad como urticaria y angioedema. Trastornos del metabolismo y la nutrición: *Raros*: hipocalcemia sintomática, a menudo en relación con trastornos predisponentes (ver sección 4.4). Trastornos del sistema nervioso: *Frecuentes*: cefalea, mareo†. *Poco frecuentes*: disgeusia†. Trastornos oculares: *Poco frecuentes:* Inflamación ocular (uveítis, escleritis, episcleritis). Trastornos del oído y del laberinto: *Frecuentes:* vértigo†. Trastornos digestivos: *Frecuentes*: dolor abdominal, dispepsia, estreñimiento, diarrea, flatulencia, úlcera esofágica*, disfagia*, distensión abdominal, regurgitación de ácido. *Poco frecuentes:* náuseas, vómitos, gastritis, esofagitis*, erosiones esofágicas*, melena†. *Raros*: estenosis esofágica*, ulceración bucofaríngea*, perforación, úlceras y hemorragias gastrointestinales altas (ver sección 4.4). Trastornos de la piel y del tejido subcutáneo: *Frecuentes*: alopecia†, prurito†. *Poco frecuentes:* exantema, eritema. *Raros:* exantema con fotosensibilidad, reacciones cutáneas intensas, como síndrome de Stevens-Johnson y necrólisis epidérmica tóxica‡. Trastornos musculoesqueléticos y del tejido conjuntivo: *Muy frecuentes:* dolor osteomuscular (óseo, muscular o articular)† (ver sección 4.4). *Frecuentes*: hinchazón articular†. *Raros*: se ha notificado osteonecrosis de la mandíbula‡ en pacientes tratadas con bisfosfonatos. La mayoría de los casos se refieren a pacientes con cáncer, pero también se han observado casos en pacientes tratadas por osteoporosis. La osteonecrosis de la mandíbula generalmente se asocia a extracción dental o infección local (como la osteomielitis). También se consideran factores de riesgo el diagnóstico del cáncer, la quimioterapia, la radioterapia, los corticosteroides y una mala higiene bucal; intenso dolor osteomuscular (óseo, muscular o articular) (ver sección 4.4). Fracturas atípicas subtrocantéricas y diafisarias del fémur (reacción adversa de clase de los bisfosfonatos)# y fracturas por estrés del fémur proximal (ver sección 4.4). *Muy raros:* osteonecrosis del conducto auditivo externo (efecto de clase del grupo de los bifosfonatos). Trastornos generales y alteraciones en el lugar de administración: *Frecuentes*: astenia†, edema periférico† *Poco frecuentes:* síntomas transitorios propios de una respuesta de fase aguda (mialgia, malestar y, raramente, fiebre), típicamente asociados con el inicio del tratamiento†. † La frecuencia en los ensayos clínicos fue similar en el grupo con medicamento y en el grupo con placebo. *Ver secciones 4.2 y 4.4. ‡ Esta reacción adversa se identificó durante la vigilancia tras la comercialización. La frecuencia de rara se estimó en base a los ensayos clínicos relevantes. # Identificada durante la experiencia post-comercialización. Notificación de sospechas de reacciones adversas. Es importante notificar las sospechas de reacciones adversas al medicamento tras su autorización. Ello permite una supervisión continuada de la relación beneficio/riesgo del medicamento. Se invita a los profesionales sanitarios a notificar las sospechas de reacciones adversas a través del Sistema Español de Farmacovigilancia de medicamentos de Uso Humano: https://www.notificaram.es. **Sobredosis.** Síntomas. La sobredosis oral puede producir hipocalcemia, hipofosfatemia y acontecimientos adversos digestivos altos, como molestias gástricas, pirosis, esofagitis, gastritis o úlcera. Tratamiento No se dispone de información específica sobre el tratamiento de la sobredosis con ácido alendrónico. Se deben administrar leche o antiácidos para fijar el ácido alendrónico. A causa del riesgo de irritación esofágica, no se debe inducir el vómito y la paciente debe mantenerse completamente erguida. **5. PROPIEDADES FARMACOLÓGICAS:** para más información consultar la ficha técnica completa. **6. DATOS FARMACÉUTICOS. 6.1 Lista de excipientes:** Goma xantana (E415), Ciclamato de sodio (E952), Sucralosa (E955), Amarillo anaranjado FCF (E110), Parahidroxibenzoato de metilo (E218), Parahidroxibenzoato de propilo (E216), Sabor a naranja con etanol e butilhidroxianisol (E320), Agua purificada. **6.2 Incompatibilidades:** No procede. **6.3 Periodo de validez:** 2 años. **6.4 Precauciones especiales de conservación:** Conservar a una temperatura inferior a 25 °C. **6.5 Naturaleza y contenido del envase:** Frasco transparente de teraftalato de polietileno (PET) con precinto de seguridad y un revestimiento de polietileno de baja densidad en tamaños de envase de 1, 2, 4 y 12 frascos. Cada frasco contiene 100 ml de solución. Puede que solamente estén comercializados algunos tamaños de envases. **6.6 Precauciones especiales de eliminación y otras manipulaciones:** Exclusivamente para un solo uso. Ninguna precaución especial para su eliminación. **7. TITULAR DE LA AUTORIZACIÓN DE COMERCIALIZACIÓN:** Laboratorios Rubió, S.A., C/ Industria, 29. Pol. Ind. Comte de Sert, 08755 Castellbisbal (Barcelona), España **8. NÚMERO(S) DE AUTORIZACIÓN DE COMERCIALIZACIÓN:** 73232 **9. FECHA DE LA PRIMERA AUTORIZACIÓN/RENOVACIÓN DE LA AUTORIZACIÓN: 10. FECHA DE LA REVISIÓN DEL TEXTO:** Abril 2016. Soludronate Semanal 70 mg solución oral (C.N. 676925; PVP: 12,01 €- PVP IVA: 12,49 €). Con receta médica. Aportación normal. Financiado por la Seguridad Social.

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- La solución oral de ácido alendrónico presenta un tránsito gastrointestinal más rápido[4]
- Mejora la tolerabilidad gástrica[3]
- Gracias a su mejor tolerabilidad y a que la solución oral accede más rápido al lugar de absorción, podría ser una buena solución para los pacientes encamados[4]

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