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Diagnosis and Treatment of Osteoporosis, an Update Bibliographic Review

Miriam Guadalupe Rodríguez Flores[1], Luis Humberto Martínez González[2], Jorge Alejandro Cruz Ponce[3], Juan Eduardo Espejo López[4], Carlos Marín Oliva[5], Isaac Montijo Ramírez[6], Abraham Azael Jaraleño Reyes[7].

[1,2,3,4,5,6,7] School of Medicine, Autonomous University of Guadalajara, Jalisco, Mexico

ABSTRACT

Introduction: Osteoporosis is a chronic, progressive skeletal disease characterized by low bone mineral density and deterioration of bone structure. There are multiple risk factors, both modifiable and non-modifiable. The main complication is fractures, which is why it must be diagnosed early and in a timely manner.

Material and methods: Fourteen articles and one book on the diagnosis and treatment of osteoporosis were chosen in order to compare the best plan to follow in these patients in the different bibliographies reviewed.

Discussion: The gold standard for diagnosing osteoporosis is the measurement of bone density with the dual energy X-ray absorptiometry device, using the T-score. The use of different biomarkers is useful both for early diagnosis and for monitoring the reaction to treatment, but it is necessary to take into account that the main objective is to prevent the disease and to improve the quality of life of the patients. On the other hand, the main and early treatment consists of physical activity adapted to each patient, diet rich in calcium, magnesium and vitamins that promote bone health, the pharmacological part of the treatment has different areas that depends on the situation of each patient, considering gender such as estrogens and progestogens in postmenopausal women, tolerance to drugs such as Denosumab, and in general, bisphosphonate is used as the first line of treatment due to the increase in bone mineral density that it produces, helping to prevent fractures and improving the quality of life of each patient.

Conclusion: Osteoporosis is one of the diseases that can prevent the realization of basic activities, for this disease there are different methods of diagnosis and treatment, the main objective is to detect risk factors and make an early diagnosis to avoid complications that entails, relying on tools such as the FRAX calculator and the use of biomarkers, all this to reach the conclusion of the investigation, to use the different options and tools to provide appropriate treatment, this publication being an update on the options that are available today to treat this condition.

KEYWORDS: Osteoporosis, bone mineral density, diagnosis, and treatment

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INTRODUCTION

Osteoporosis is a chronic and progressive skeletal disease characterized by decreased bone mineral density (BMD) and deterioration of bone structure. This results from an imbalance in the process that maintains the rate of bone remodeling mediated by osteoclasts, osteoblasts and osteocytes. The most common risk factors include having a history of hip fracture, being older than 65 years, female sex, early menopause (before 45 years of age), continuous systemic steroid use for more than 3 months, having a body mass index (BMI) less than 19 kg/m2, alcohol and/or tobacco use, among others.

It is estimated that osteoporosis is a global disease that affects 200 million people worldwide, causing approximately 9 million fractures per year, being those of the vertebrae and proximal femur the most frequent. It is the most prevalent bone disease in patients over 50 years of age, in the United States there are approximately 40 million people suffering from osteoporosis, each year there are about 300,000 hip fractures, most of which require hospitalization and surgery.

There are two types of etiology:

Primary osteoporosis: This type is related to age and sex hormone deficiency.

Secondary osteoporosis: It is caused by some disease and/or comorbid medications such as glucocorticoids.

Although osteoporosis is more common in the female sex due to post-menopausal hormonal changes, men tend to develop more fractures secondary to this disease, due to the fact that statistically male patients are involved in activities with higher risk of presenting bone lesions. The most common and serious complication is the hip fracture since it affects the physical functionality of the patients, only 20% will be able to perform basic tasks after suffering this type of fracture, 40% will not usually recover the functionality they had before and 62% will require nursing services at home. That is why an early and timely diagnosis is needed to reduce complications and give the patient a better quality of life.

Unfortunately, this disease is asymptomatic until a fracture occurs, therefore, it is considered a silent disease and here lies the importance of considering the risk factors to perform preventive studies.

THEORETICAL FRAMEWORK

The diagnosis of osteoporosis can be made with different studies; however, it is essential to take a good medical history that can guide the doctor to a diagnosis and thus rule out some differential diagnoses. This document should include important aspects of the patient such as family history, previous surgeries, lifestyle and evaluate their risk factors to see if there is a possibility of having this disease. Similarly, the physical examination should be considered since there is evidence that

overweight is an important risk factor for osteoporosis. The loss of height should also be verified, since if it has decreased, this would indicate that there

may be vertebral compression due to fractures.[1]

As for studies that can be performed, the gold standard is the measurement of bone mineral density (BMD) which is done with a dual energy X-ray absorptiometry (DXA) device and mainly takes as anatomical points the hip and lumbar spine. [2]

Indications for bone density measurement are: [3]

- Women over 65 years of age and men over 70 years of age, regardless of whether or not they have clinical risk factors.
- Younger postmenopausal women, women in menopausal transition and men aged 50-69 years with clinical risk factors for fracture.
- Adults who had a fracture at age 50 or later.
- Adults with disorders such as rheumatoid arthritis or receiving any drug that are accompanied by small bone mass or bone loss.

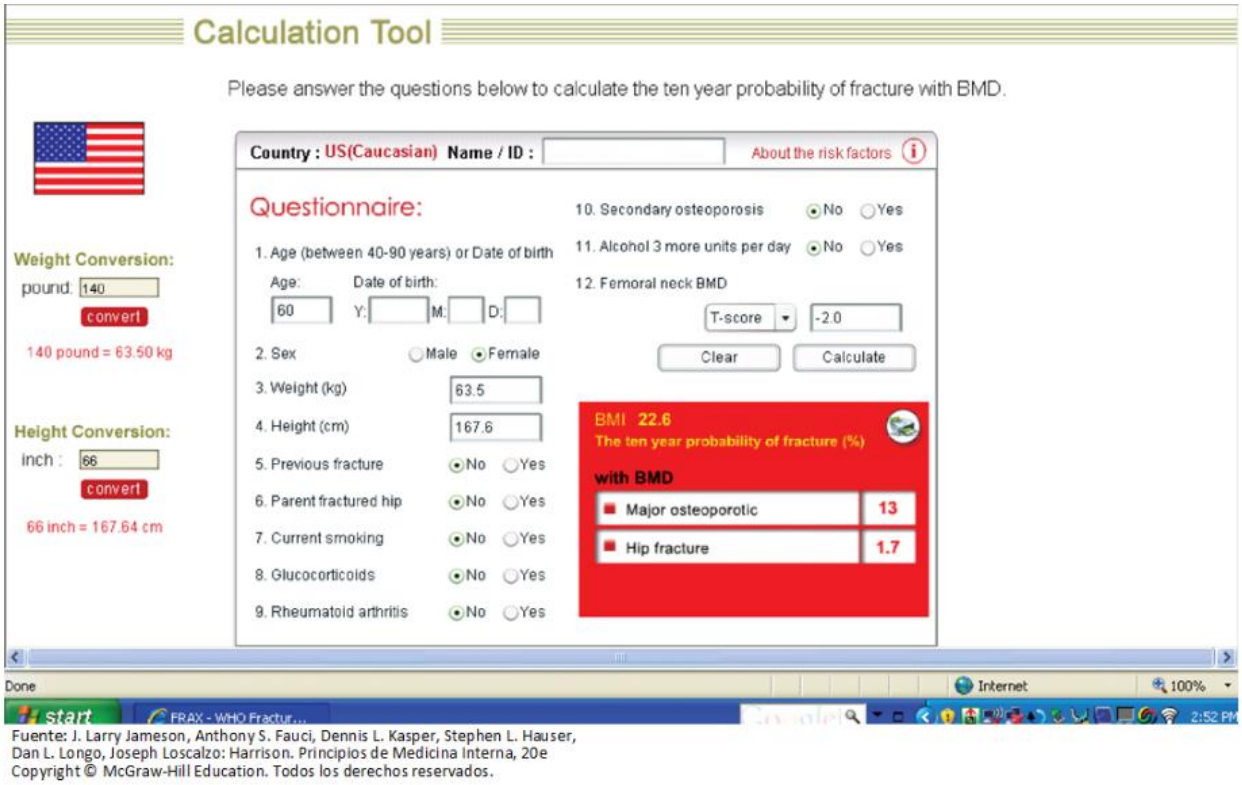
According to the World Health Organization (WHO), BMD is interpreted with T-scores, depending on these values is how we know if the patient has absence of the disease, osteopenia, and osteoporosis or suffers from severe osteoporosis, as shown in Table 1.[2]

Table 1.T-Score scores along with their diagnostic interpretation. [2]

Interpretation	Score T
Normal	-1.0 and higher
Osteopenia	-1.0 a -2.5
Osteoporosis	-2.5 and lower
Severe osteoporosis	-2.5 and under with one or more fragility fractures

It is recommended that all adults over the age of 50 with a history of fractures have a bone mineral density screening. The Endocrine Society suggests screening all men over the age of 70 who do not have risk factors and those who do have risk factors are suggested to be screened starting at age 50-69. [2]

Another way to diagnose osteoporosis was developed by the University of Sheffield, is the Fracture Risk Assessment Tool (FRAX). It should be done starting at age 50 or in women at the onset of menopause. This tool measures risks such as age, race, alcoholism, sex, BMI, smoking, glucocorticoid use, family, or personal history, among others. [4] As attached below in image 1.



Fuente: J. Larry Jameson, Anthony S. Fauci, Dennis L. Kasper, Stephen L. Hauser, Dan L. Longo, Joseph Loscalzo: Harrison. Principios de Medicina Interna, 20e

Image 1. FRAX calculation tool [3]

Although DXA is used to obtain lateral images of the dorsal and lumbar spine, the images are not of very good quality as those of radiographs, for this reason it is suggested in some patients to perform radiographs, in addition to the fact that it is frequent that patients with osteoporosis have asymptomatic vertebral fractures. The indications for spine imaging studies are listed in Table 2**.** [3]

Table 2.Indicaions for imaging studies of the spine [3]

Consider spinal imaging studies
In females >70 years and males >80 years if the T-score on bone density testing at the spine, full hip or femoral neck is <1.0
In females aged 65-69 years and males aged 70-79 years if the T-score on bone density testing at the spine, full hip or femoral neck is <1.5
In postmenopausal women and men >50 years with specific risk factors: • Fractures due to minor trauma • Decrease in historical height of >4 cm • Prospective decrease in length of >2 cm • Recent or long-term constant glucocorticotherapy

Biochemical markers are used in this disease because they are sometimes useful to estimate fracture risk in advance, apart from bone density. Their main function is to monitor response to treatment. The best biomarker is said to be carboxy-terminal telopeptide of type I collagen (CTX), as at 3-6 months it gives an early estimate of the patient's response to treatment. However, there are other biomarkers shown in Table 3. [3]

Table 3. Bone metabolism biomarkers [3]

Bone formation
❖ Serum bone-specific alkaline phosphatase ❖ Serum osteocalcin ❖ Serum procollagen type I propeptide
Bone resorption
● Urinary and serum cross-linked N-telopeptide ● Urinary and serum cross-linked C-telopeptide

Speaking of innovative diagnostic alternatives, there is radiofrequency ultrasound multiple spectrometry (REMS) that can be used in the femoral neck. A cross-sectional observational study was carried out involving 1,914 postmenopausal female patients aged 51-70 years with a BMI <40 and no significant impairment of ambulation. REMS was used in the lumbar region where the ultrasound transducer was placed in a transabdominal position below the sternum, starting with the L1 to L4 vertebrae; femoral vertebrae were also explored where the ultrasound transducer was placed parallel to the head-neck axis of the femur. In this study the patients were divided into three categories: osteoporosis, osteopenia and healthy. It was found that this diagnostic study has more specificity in comparison with DXA evaluating the lumbar and femoral bones of the patients.[5]

Quantitative ultrasound (QUS) uses changes in sound velocity and broadband ultrasound attenuation to obtain approximate BMD. The recommended anatomical reference site is the calcaneal bone as this is mostly cancellous bone. This study was carried out in 82 patients of both sexes in which the DXA was compared with the QUS, for which first the lumbar and hip DXA was performed in the patients and then proceeded with the QUS. The results showed that with this diagnostic method (QUS) together with the symptoms of the patients, an early diagnosis of osteoporosis can be speculated and thus be able to start with general measures to maintain the patient's health while more specific studies are carried out. [6]

On the other hand, microRNAs (MiRNAs) are endogenous non-coding RNA molecules that regulate post-transcriptional gene expression through mRNA targeting and regulate bone formation and resorption, which is why MiRNA irregularities contribute to the onset and progression of bone disorders such as osteoporosis. In Iraq, MiR-133a and MiR-25 are used as biomarkers in patients with osteoporosis. MiR-133a regulates muscle cell differentiation and plays an important role in the regulation of the skeletal muscle system. MiR-25 has an effect on osteoblasts where it favors their survival. [7]

A 2016 study in Kocijan evaluated MiRNAs in patients with idiopathic or postmenopausal osteoporotic fractures of both sexes and found that these molecules are excellent at discriminating fractures. MiR-133a has been subjected to several studies where it has been found to be decreased in women with osteoporosis who underwent a 12-month treatment with teriparatide. Another study showed that MiR-25-3p is a key post-transcriptional regulator of osteoclast differentiation and negatively regulates osteoclast function through nuclear factor IX. As a result of these studies, it was concluded that there is still much to be investigated, however, MiRNAs can be used as early diagnostic tools and in the not-too-distant future they can be used for therapeutic purposes. [7]

It is known that osteoporosis is a progressive disease and that is why a complete treatment plan must be carried out. That is why management is divided into universal recommendations which consist of exercise, where a healthy state of strength and posture must be maintained to prevent falls. Such exercises include running, muscle strengthening with weightlifting, however, it should be noted that this type of exercise should be performed under the supervision of a professional and of moderate intensity especially in women >70 years to prevent risk of falls and injury**.** [8]

Nutrition is very important as there is evidence that macronutrients and micronutrients help in the prevention and treatment of osteoporosis.

Speaking of macronutrients such as proteins, they have several benefits which are encompassed in 3 main groups:

1. They form a large part of the organic bone matrix.
2. They regulate serum levels of insulin-like growth factor 1.
3. They affect calcium metabolism. [9]

Because of this, a daily intake of animal protein of 0.8 g/kg of body weight is recommended for young adults and 1.0 g/kg of body weight for older adults. As for lipids, it is advisable to ingest saturated fatty acids which are found mostly in seafood as it is one of the main sources of polyunsaturated fatty acids, these increase BMD thus reducing the risk of fractures, which is why they are important in the diet. Water-soluble fiber is beneficial because it has a high calcium retention effect in the bone. [9]

Micronutrients such as calcium and vitamin D are the cornerstones in the treatment of this disease. It is said that vitamin D is one of the most important supplements to maintain a good state of health since it helps the small intestine to absorb calcium through 7-dehydrocholesterol which is modified to previtamin D3 by the liver and in the

kidneys results in its final form which is calcitriol. When prescribing this vitamin, the physician must consider the renal or hepatic functioning of the patient due to the same mechanism of action that this vitamin has, if either of these two organs is not functioning properly, its effectiveness will be compromised. Alfacalcidol is an analog of vitamin D3 that has the capacity to be converted into calcitriol when it has renal activity or to be activated directly in the bone where it increases mineralization. Alfacalcidol has proven to be a good complement to different treatments for osteoporosis such as bisphosphonates, since it increases bone density and reduces the risk of fractures. It should be considered that both calcitriol and Alfacalcidol have the risk of causing hypercalcemia, in spite of this, both have the approval to be used as a therapeutic method. [10] The foods from which we can obtain vitamin D are egg yolk, seafood, cod liver oil and cereals. [7] The required intake of vitamin D is 800 IU per day. [2]

Calcium supplementation is essential as it optimizes vitamin D absorption. [4] The daily dose of calcium in men between 50-70 years of age should be 1,000 mg and in women >51 years of age it should be 1,200 mg per day, never exceeding 1,500 mg. [6] The main sources of calcium are dairy products, salmon, almonds, green leafy vegetables, among others. [7]

Magnesium deficiency can impair bone health by enhancing osteoclasts and reducing osteoblast function. This is why a daily intake of 320 mg in women and 420 mg in men is recommended. It can be obtained from green vegetables, legumes, nuts, seeds, whole grains, and almonds. [9]

The physician should tell osteoporotic patients that they should eliminate tobacco consumption, reduce alcohol consumption, and have their homes conditioned to prevent falls, i.e., their homes should have proper home lighting, handrails on stairs, handrails in bathrooms, and if the patient has balance problems or weakness, the use of a cane or walker should be implemented. [11]

On the other hand, the objective of giving medication to patients with osteoporosis is to reduce the risk of fractures. There is a therapeutic method known as "sequential treatment", which is that after using a treatment for a long period of time, it should be suspended and/or substituted by another drug in sequence for the following reasons: [12]

A. Osteoporosis is a chronic disease that requires long-term treatment.
B. Most drugs contain a maximum recommended duration.
C. The longer the patient consumes a drug, the higher the risk of complications.
D. If a drug is discontinued and not replaced by another there is a decrease in BMD.
E. If a drug is used for a long period of time, it is more likely that its efficacy will not be adequate.

In menopausal women it has been concluded that estrogens alone or together with progestogens, act by activating nuclear estrogen receptors, whose stimulation inhibits osteoclastogenesis through inhibition of the nuclear factor Kappa B activating receptor and stimulation of osteoprotegerin, and effects on osteoformation have been found. Discontinuation of estrogen can lead to increased remodeling, with a rapid decrease in bone mineral density and increased risk of fractures that can be prevented by administering bisphosphonates. [12]

Selective estrogen receptor modulators are drugs that inhibit resorption and antagonize estrogen receptors in the breast and endometrium, resulting in positive estrogenic effects in patients with osteoporosis and reducing adverse effects. In women with postmenopausal osteoporosis, Raloxifene and Bazedoxifene increase bone mineral density and reduce the risk of vertebral fracture. Upon discontinuation of this drug there is loss of bone mineral density in the lumbar spine and femur. [12]

Bisphosphonate is an antiresorptive agent (it has high affinity to bone for hydroxyapatite crystals). [13] It is the first line for the prevention and/or treatment of osteoporosis. It should be taken on an empty stomach in the morning with a glass of water and the patient should be told that it is necessary to wait 30 minutes before ingesting any type of food. [8] Alendronate, Risedronate and zoledronic acid increase BMD and thus decrease the risk of fractures. Table 4 below shows the doses of the different bisphosphonates.

Table 4. Prophylactic and treatment doses of bisphosphonates [2]

Bisphosphonate	Prophylactic doce	Treatment dose
Alendronate	5 mg orally once a day or 35 mg orally once a week	10 mg orally once a day or 70 mg orally once a week
Risedronate	5 mg orally once a day or 35 mg once a week	5 mg orally once a day or 35 mg orally once a week or 150 mg orally once a month
Zoledronic Acid	5 mg intravenously every 2 years	5 mg intravenously once per year

The mechanism of action of Denosumab is to inhibit osteoclastogenesis without depending on renal function. [13] It is recommended especially in patients with a high risk of fractures and for patients who cannot take oral medication since it is administered subcutaneously 60 mg every six months, it is used to reduce bone resorption. It is important to

know that before administering Denosumab, calcium levels should be corrected in patients since this drug usually causes hypocalcemia. [2]

Raloxifene reduces bone resorption and increases BMD. It is a treatment for patients at high risk of fractures. Its dose is 60 mg per day. Its adverse effects are venous thromboembolism, vaginal bleeding, cardiovascular disease, among others. Its administration should be avoided in female patients with a history of active thromboembolism, premenopausal, pregnant, or breastfeeding. [2]

Calcitonin is a synthetic polypeptide hormone that can be obtained from mammals, birds, and fish. It has been approved for use in postmenopausal women with osteoporosis when alternative treatments are not feasible. It is administered as a spray into one nostril per day, alternating nostrils each day. [2]

Teriparatide is a recombinant human PTH analog. It stimulates new bone formation by stimulating osteoblasts. It is suggested in patients with previous fragility fractures or at high risk of fracture and for patients who cannot take oral medications. The recommended dose is 20 mcg SC once a day in the thigh or abdomen, administered subcutaneously. [2]

A study was carried out in which the objective was to compare Denosumab with 15 other drugs (Alendronate, Risedronate, Ibandronate, Zoledronate, etidronate) against osteoporosis. As a result, more than 85% showed that the cost-effectiveness of Denosumab is superior compared to Risedronate in patients >70 years of age. Also, Denosumab was better compared to Raloxifene and Ibandronate in patients >65 years old. Finally, it is mentioned that there was a comparison with Alendronate in patients 65-75 years of age in which Denosumab was 65% better than Alendronate. Therefore, it was concluded that Denosumab has a good cost-effectiveness ratio in elderly patients, with a history of fractures, a low BMI, among other factors. [14]

In Mexico the main drugs used for osteoporosis are Teriparatide and Denosumab. Teriparatide is an anabolic hormone that is indicated in patients with severe osteoporosis who have previous hip or vertebrae fractures, it is also prescribed when the patient did not have good results with Calcitriol or Bisphosphonates. This is why a systematic review was carried out in which it was concluded that the reduction in the risk of vertebral fractures was greater with Teriparatide (9.3%) than with Denosumab (4.8%). The risk reduction of non-vertebral fractures was also greater with Teriparatide (53%) compared to Denosumab (20%). [15]

An investigation was carried out in which 4093 postmenopausal women with osteoporosis and fragility fractures were treated with Romosozumab 210 mg or Alendronate 70 mg for 12 months. The incidence of new vertebral fractures in the last 24 months and the number of non-vertebral fractures were considered, as well as the adverse effects such as cardiovascular effects, mandibular osteonecrosis, and atypical femoral fractures. In a period of 24 months, it was obtained as a result that the patients who were administered Romosozumab had a 48% lower risk of having new vertebral fractures. Fractures occurred in 198 patients out of 2046 in the Romosozumab group and 266 out of 2046 patients using Alendronate, so the risk of fracture administering Romosozumab is 19% compared to 38% for Alendronate. [16]

Therapeutic vacations

This means that treatments are suspended for a period of time in order to reduce long-term complications or improve the response to treatment. As in the case of bisphosphonates, when taking them for a prolonged period of time, they should be suspended for at least 5 years when taken orally, but only in patients <70 years of age, who do not have fractures, who do not have decreased BMD in the hip, who do not present risk factors for fractures or a high risk according to FRAX. [12]

MATERIAL AND METHODS

This article was conducted through a research based on several books such as: "Harrison's Principles of Internal Medicine", "Clinical Diagnosis and Treatment", in addition to articles obtained from "Clinicalkey", "Elsevier", "Springer". Fourteen articles and two books on rheumatoid arthritis were chosen in order to identify the most accurate diagnostic methods and the most effective and innovative treatments.

DISCUSSION

The research makes a general approach to the different diagnostic and treatment methods for osteoporosis. Among the diagnostics it should be noted that the gold standard is the measurement of bone mineral density using DXA, for this study the T-score is used as a means of interpretation where the patient will be considered to have osteoporosis from a value equal to or less than 2.5. It has also been demonstrated that MicroARNS are present in the bone catalytic process, these biomarkers are not only useful in the diagnosis, but can also support the monitoring of the response to treatment. Quantitative ultrasound (QUS) together with the clinic gives us a presumptive diagnosis of osteoporosis and thus, it is possible to initiate general measures in patient care. Likewise, radiofrequency echo multiple spectrometry (REMS) has better results in the evaluation of lumbar and frontal compared to DXA.

On the other hand, treatment is divided into two parts, the first consists of a non-pharmacological plan, which includes low-impact physical activity with the aim of strengthening muscles and posture, this will prevent falls that may affect the patient; the diet should contain essential macronutrients such as proteins and lipids, as well as micronutrients such as calcium, vitamin D and magnesium. The second line of treatment is pharmacological, as part of this, estrogens, progestogens, and selective estrogen receptor modulators are the best choice in postmenopausal female patients, acting

against the disease by inhibiting osteoclast genesis, stimulating osteoprotegerin and osteo-formation. The first line of treatment for osteoporosis is the bisphosphonate is considered the first line of prevention and / or treatment, the aforementioned are antiresorptive with the aim of increasing BMD and thus reduce the risk of fracture. Denosumab is recommended in patients at high risk of fractures or who do not tolerate OV or Teriparatide, which is also recommended in cases of a history of fragility fracture. Finally, we have Calcitonin which is used in women in whom other treatments are not viable and Romosozumab which proved to be more effective than Alendronate but increases the number of vascular accidents, so care must be taken in its indication.

CONCLUSION

Osteoporosis is a chronic and silent disease until it produces a fracture, which can have serious consequences if not diagnosed and treated early. Clinical history and risk factor assessment are the first line for early diagnosis of osteoporosis, and the FRAX calculator comes in as a very useful tool to guide the initial evaluation. In addition to this study the use of bone mineral density measurement with DXA, which to this day remains the gold standard for the diagnosis of osteoporosis. In this study we searched for new diagnostic techniques where MicroRNAs showed potential as a diagnostic marker and as a marker of response to treatment. QUS was found to be usable as a presumptive diagnosis and REMS proved to be the best technique for evaluation of lumbar and frontal bones.

The treatment of this disease should be multidisciplinary, both non-pharmacological and pharmacological. Regarding the first point, low impact exercise and diet with calcium and vitamin D supplements will help us to have a better control and management of the disease. As pharmacological management, bisphosphonates are used as the first line of management, however, denosumab is another drug that is frequently used but is reserved in cases with severe osteoporosis. There are other drugs such as teriparatide, its use should be relegated to certain patients as well as selective estrogen receptor modulators and estrogen therapy in monotherapy or combined with progestins, each therapeutic option should be used with caution and individualize the treatment to each patient due to the adverse effects that this entail, the physician should adapt the therapeutic management to the needs of each patient.

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