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REVIEW ARTICLE

Bone health in patients with prostate cancer†

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Abstract
Context: In patients with prostate cancer, bone health is compromised by advanced age at diagnosis, androgen suppression treatments and the development of bone metastases. In this paper the medical literature is reviewed in order to update the state of the art on their incidence, prevention and management.
Evidence acquisition: A literature review about bone involvement in patients with prostate cancer in different clinical settings is performed.
Synthesis of the evidence: Decreased bone mineral density is higher in patients diagnosed of prostate cancer before starting treatment than in healthy men with the same age. During the first year of treatment, a severe loss of bone density is reported due to androgen suppression therapy. From then on, loss of bone density seems to slow down, persisting at long-term. It is important to know the starting point and the dynamics of bone loss in order to prevent its progression. The skeletal events have an important impact on quality of life in patients with prostate cancer. Both denosumab and zoledronic acid have proven effective in reducing bone loss.
Conclusions: The prevention and management of bone involvement in patients with prostate cancer are critical to quality of life in these patients and require an individualized approach. Before starting a prolonged androgen deprivation, baseline risk of fracture should be evaluated in order to adopt the proper protective measures. In patients with metastases, early treatments reducing the risk of bone events should be taken into account.

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Salud ósea en pacientes con cáncer de próstata

Resumen

Contexto: La salud ósea se ve comprometida en los pacientes con cáncer de próstata por la avanzada edad media al diagnóstico, los tratamientos de supresión androgénica y el desarrollo de metástasis óseas. Revisamos la literatura con la finalidad de actualizar el estado del arte sobre su incidencia, prevención y manejo.

Adquisición de la evidencia: Realizamos una revisión de la literatura sobre afectación ósea en los pacientes con cáncer de próstata en diferentes contextos clínicos.

Síntesis de la evidencia: Los pacientes diagnosticados de cáncer de próstata experimentan una disminución de la densidad mineral ósea mayor que varones de la misma edad antes de iniciar el tratamiento. La supresión androgénica provoca una pérdida de masa ósea más intensa durante el primer año de tratamiento, y parece ralentizarse a partir de entonces, persistiendo a largo plazo. Conocer del punto de partida y de la dinámica de la pérdida de masa ósea es importante para prevenir su progresión. Los eventos relacionados con el esqueleto ejercen gran impacto en la calidad de vida de los pacientes, y tanto el denosumab como el ácido zoledrónico han demostrado ser eficaces en su reducción.

Conclusiones: La prevención y el manejo de la afectación ósea en pacientes con cáncer de próstata es determinante para su calidad de vida y exige un abordaje individualizado. Antes de iniciar una supresión androgénica prolongada debe valorarse la situación de riesgo basal del hueso para adoptar las medidas protectoras apropiadas. En aquellos con metástasis debe considerarse precozmente el inicio de terapias que disminuyan el riesgo de eventos óseos.

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Context

Prostate cancer (PCa) is the most frequent cancer among men and accounts for one of the most prevalent neoplasms in the Western world. According to data supplied by GLOBO-CAN, the estimated incidence and mortality for 2008 in Europe were 94 new cases and 12 deaths per 100,000 men-year.1 Data from the Spanish register 2010, on a sample of 21% of the population, give an estimated incidence rate of 82.27 per 100,000 men. Although around 4% of the patients with PC have metastases at diagnosis, nearly 40% will be eligible for androgen suppression therapy (AST) due to the presence of metastasis itself, as a concomitant therapy to radiotherapy or by complementing any previous radical treatment after biochemical recurrence.2

Bone, which is involved in over 80% of metastatic cases,3 is the most frequent metastatic location for PCa. The main complications of these metastases (pain, spinal cord compression, fractures) add significant morbidity and a significant reduction in quality of life.

The significant number of patients who will receive prolonged AST, the advanced mean age, which is already a risk factor for the development of osteopenia or osteoporosis, and metastatic involvement are determinants of bone health care being crucial in the overall management of these patients.

Evidence acquisition

We conducted a review of the unstructured literature of those relevant published articles regarding the bone health of patients with PCa from a global perspective. To this end, we analyzed its impact on the different situations in which it is involved: at diagnosis, given the advanced mean age, as a result of AST and in a situation of bone metastasis.

Synthesis of the evidence

Hypogonadism and osteoporosis

In adults, a healthy bone is in a constant process of remodeling, with a balance between resorption and bone formation, mediated by the action of osteoblasts and osteoclasts, as well as numerous hormones, calcium levels, vitamin D, growth factors and cytokines, among others. Estrogens appear to be the determinant steroid hormone in the regulating process of bone resorption.4 The testosterone that reaches the bone is converted into estrogens by aromatases. Therefore, hypogonadic males, whatever their origin, show marked estrogen deficiency, thus causing an imbalance in bone remodeling.3

Estrogen deficiency induces the production of proinflammatory cytokines such as TNF and IL 6 and the stimulation of the RANK and RANKL system, membrane ligands which activate osteoclast proliferation and differentiation from their precursor cells in the bone marrow.4 Simultaneously, estrogen shortage blocks the transcription of osteoblast growth factors, which leads to a decrease in their activity and an increase in their apoptosis.

These factors condition a predominance of bone resorption, which results in a decreased bone mineral density that significantly increases the risk of fractures.

Osteoporosis associated with prostate cancer

Bone morbidity in patients with PCa is significant and is associated with epidemiological reasons, such as age,
hypogonadism secondary to AST and the appearance of bone metastases.

Patients diagnosed with PCa have a greater decrease in bone mineral density (BMD) than that observed in other men of the same age before starting any treatment. The presence of osteopenia has been confirmed in around 30−40% of cases, osteoporosis in 5−10% and a history of fractures in 9%.2

Besides, AST increases bone resorption, reduces BMD and increases the risk of fractures in men with PCa, which may imply a major cause of morbidity.6,9 It is estimated that one in every four men with PCa over the age of 50 under hormonal treatment will experience a skeletal event, understood as the appearance of fractures, need for surgery or radiotherapy or spinal cord compression.10 The fracture rate due to osteoporosis attributed to AST in patients with PCa is somewhere between 5 and 40%, depending on the duration of suppressive therapy and the follow-up time of the sick.

Clinical relevance of osteoporosis in patients with prostate cancer

Hip fracture is the most serious complication of osteoporosis, since it is accompanied by a significant morbidity and mortality. Only 41% of men who survive a hip fracture recover their previous level of vitality and 79% require any kind of health care a year later. The mortality rate a month after hip fracture is 16%, 4 times greater than that described in women, and one in every 3 men dies within the first year. Oefeleinet al. detected a negative association between skeletal fracture and overall survival in a group of 192 patients with PCa who had undergone AST.11

Quantification of bone mass loss and risk of fracture

Before starting AST, the American National Osteoporosis Foundation (NOF) recommends evaluating the condition of bones through bone densitometry and determining their history of femur and vertebral fractures.12

The locations where, due to a greater proportion of trabecular bone, BMD should be assessed are the vertebral bodies, the femoral neck and the distal third of the radius.

Although there are currently several methods available to determine BMD, dual-energy X-ray absorptiometry (DXA) is the most accurate and location-specific test, which is being considered as the standard technique, with a sensitivity and specificity of 96%.

Osteoporosis is a skeletal disorder characterized by reduced bone strength which increases the risk of fractures. Bone strength depends on BMD and bone quality. Osteoporosis is caused by 3 different mechanisms: an inability to achieve an adequate mineral mass, excessive bone resorption or altered bone formation.

The results of the bone densitometry procedure are assessed by using T-score, which represents the number of standard deviations where the patient’s estimated BMD deviates from the mean of healthy individuals of the same age. According to World Health Organization (WHO) criteria, a value of −1 standard deviation is considered normal, although it represents a 10−12% of bone mass loss when compared to the healthy population, with a 1.5- or 2-fold greater risk of fracture. A T-score between −1 and −2.5 defines osteopenia, a T-score less or equal to −2.5 is diagnostic of osteoporosis, whereas the presence of a fracture defines severe osteoporosis.13

Characteristics of bone mass loss in patients receiving androgen suppression

AST through chemical or surgical castration causes a sharp fall in the serum levels of testosterone and estradiol.8 This new hormonal scenario has a great impact on bone remodeling, in such a way that there is a bone mass loss of around 5% throughout the first year of treatment.14 It is a significant body mass loss, since healthy adult men lose around 0.5% each year and postmenopausal women around 1% and 2%, depending on their age.15 In fact, this bone mass loss induced by castration is only exceeded in the following 2 situations: in postmenopausal patients simultaneously treated with aromatase inhibitors and LHRH agonists where 7.4% of it is lost, and in women with premature menopause induced by chemotherapy where bone mass loss accounts for 7.7%16 (Fig. 1).

Only one longitudinal study has analyzed the dynamics of bone mass loss in castrated patients depending on time during the first 2 years.17 This study highlighted that the greater loss occurs within the first year of treatment, with its intensity decreasing over the second year in all skeletal locations (Fig. 2).

A cross-sectional study analyzed the prevalence of osteoporosis throughout a 10-year period with AST and indicated that the osteoporosis rate before starting AST was 35% and reached 80% 10 years after treatment.18 This suggests that, although bone mass loss slows down from the second year on, this loss persists at least up until year 10.

Knowledge of the starting point and of the dynamics of bone mass loss in patients with PCa has clinical relevance, since it implies a need for assessing the status of BMD before starting AST and for the implementation of preventive measures, particularly during the first year of treatment.

Prevention and treatment of bone mass loss during androgen suppression

The NOF recommends certain lifestyle and dietary standards to patients at a risk for fractures due to bone mass loss12 (Table 1). It should be emphasized that the recommendations for a daily calcium and vitamin D intake are not fulfilled by a high proportion of patients with PCa receiving AST.19

Once the status of BMD of a specific patients has been assessed, the indication for antiresorptive treatment would be established in any patients with a history of fracture, presence of osteoporosis in the bone densitometry or of osteopenia associated with a 10-year risk of hip fracture over 3% and of major osteoporotic fracture over 20% (Fig. 3; Table 2).

In the specific case of patients candidate for receiving AST, we would recommend considering alternatives to castration, such as monotherapy with antiandrogens or
Figure 1  Bone loss induced by androgen deprivation therapy in connection with other physiological and pathological conditions.

Figure 2  Loss of bone mass during the first year of androgen suppression.

Table 1  Hygienic and dietary measures recommended in patients undergoing androgen suppression.

| Healthy dietary habits and supplements of calcium and vitamin D that ensure a daily intake of more than 1200 mg and vitamin D between 800 and 1000 IU |
| Suppression of tobacco and alcohol |
| Maintained exercise and not aggressive |
| Considering forms of androgen suppression that do not reduce the bone mass or at least minimize it: monotherapy with antiandrogens, intermittent androgen suppression |
intermittent AST, which are hormonal therapy forms that do not induce bone mass loss or do so with less intensity.20,21

The pharmacological treatment with antiresorptives has been little studied in patients with PCa undergoing AST. At present, only denosumab (60 mg subcutaneous/6 months) is accepted as preventive treatment for fractures associated with AST in patients with PCa and an increased risk of fracture. It is a fully human monoclonal antibody with high affinity and specificity due to RANKL, which neutralizes its activity. Its administration versus placebo has shown an increase in BMD of around 6% and a reduction in the risk of new vertebral fractures of 60%.9

Toremifene (80 mg oral/day) in patients with PCa receiving AST and a high risk of fractures has also shown to increase BMD with a reduction in the risk of fractures of 50%. However, this being a rare event (2.6%), it increases to double the risk of thromboembolic phenomena.10

Other active substances, such as intravenous zoledronic acid (4 mg IV/3 months or annual) or alendronate (70 mg oral/weekly), have proven effective in the reduction of bone density loss, although they are not approved for that indication.

**Prevention of bone metastases in prostate cancer**

Given the predilection of PCa metastases for bone tissue and certain favorable results observed at a preclinical level, the antitumor and antitumorstatic effect of certain bone-targeting agents in non-metastatic patients is being investigated, either as monotherapy or in combination with other agents, with the aim of delaying disease progression.22

Due to the key role of RANKL in the physiopathology of bone metastases in PCa, denosumab has also been studied for that purpose.23 A phase III trial that randomized between denosumab and placebo in 1432 patients with castration-resistant tumors and a high risk of bone metastases (PSA > 8, PSA doubling time ≤ 10 months, or both) showed that denosumab managed to significantly extend the bone-metastases-free interval (median 29.5 versus 25.2 months; relative risk: 0.85, CI 95% [0.73–0.98]; p = 0.032), this benefit being particularly relevant in the subgroup of patients with a PSA doubling time < 6 months.24,25 Symptomatic bone metastases were reported in 10% of the patients with denosumab versus 13% of those treated with placebo (p = 0.03) and survival was comparable. Side effects were similar in the 2 groups, except for osteonecrosis of the jaw and hypocalcaemia, which were seen more often in the denosumab group (5 and 2% respectively) than in the placebo group (0% and < 1% respectively).24

The evidence does not appear to be sufficiently significant to recommend any preventive treatment.

**Treatment of bone metastases**

As in any other neoplasm with secondary bone involvement, palliation of symptoms and maintaining the best quality of life possible are the main aims of therapy. Pain, functional impotence due to fracture and compressive spinal
cord involvement are serious complications, with a generally positive therapeutic response to AST in patients previously untreated. Unfortunately, the same complications accompany the sick in their final castration-resistant phase, where bone metastases condition their quality of life. In this phase of the disease, the involvement of a multidisciplinary team including radiotherapists, orthopedic surgeons, neurosurgeons, rehabilitologists, specialists in nuclear medicine, psychologists, pain specialists and trained nursing staff for support, will help the patient minimize the deterioration in his quality of life.

The approved therapeutic options for the treatment of bone metastases due to PCa are the following ones.

**Hormone therapy and chemotherapy**

AST, in any of its forms, is the gold standard of initial treatment for PCa with symptomatic bone metastases with a positive response, at a radiological and clinical level, in over 80% of cases. Abiraterone along with prednisone, in oligosymptomatic metastatic castration-resistant patients (PCRC) prior to chemotherapy, has demonstrated benefit in survival and radiological progression versus the placebo–prednisone combination in the phase III study COU-AA-302. In this same study, 83% of patients had bone disease, 47% of whom with over 10 cancer deposits. Abiraterone demonstrated a reduction in radiological progression with a significant increase in the elapsed time until starting opioids for pain control when compared with the other arm (HR = 0.69).

Similarly, abiraterone in PCRC (phase III study COU-AA-301) demonstrated superiority over placebo in terms of overall survival and radiological progression of the disease in patients with metastatic bone involvement in 90% of cases and a mean of 3.0 points (0–10) on the BPI-SF scale.

For its part, enzalutamide (MDV-3100), compared with placebo in patients with metastatic PCRC after progression to docetaxel, has also shown a delay to the first SRE of 3.4 months with a risk reduction of 31%.

**Chemotherapy**

Docetaxel and cabazitaxel, in patients with PCRC, are the only chemotherapy drugs that have shown a significant increase in overall survival, but not in relation to decreased pain or in the progression time to bone pain.

**Bisphosphonates**

Zoledronic acid (4 mg IV/3–4 weeks) combined with calcium and vitamin D for the prevention of skeletal events, including fractures, spinal cord compression, surgery and radiotherapy, is approved in the US for the treatment of PCRC with bone metastases. In Europe, the EMA approval includes all patients with bone metastases, regardless of their hormonal status. Both benefits and risks must be considered, especially with regard to the appearance of osteonecrosis of the jaw. With regard to controlling bone pain, it has shown a maintained benefit with a significant improvement in pain parameters at rest, in motion and with respect to functional mobility.

**Monoclonal antibodies**

Denosumab (120 mg subcutaneous/4 weeks) has proven superior to zoledronic acid, having been approved by the EMA and FDA for the prevention of skeletal events in patients with solid tumors and bone metastases. Equally, it must be combined with calcium intake and vitamin D and the risk of osteonecrosis of the jaw must be considered.

Patients with bone metastases should undergo therapy with antiresorptives, zoledronic acid or denosumab, depending on the individual risk profile, in order to decrease the likelihood of developing skeletal events; the greater the pain, the spread of the disease or the presence of osteopenia or osteoporosis, the earlier the treatment should be started (Figs. 4 and 5).

**Radiopharmaceuticals**

The use of intravenous radiopharmaceuticals has shown clinical utility in the management of patients with multiple painful metastases and with persistent pain despite treatment with radiotherapy, its use being advisable before pain becomes intractable. Agents such as samarium-153, rhenium-186 and radium-223 are able to attach themselves to areas of osteoblast activity irradiating adjacent tumor cells and cytokine-releasing cells which mediate in bone pain with a variable antalgic response. Myelosuppression is its most important toxic effect, and is more prominent with strontium than with samarium. Radium-223 is an alpha particle emitter that has demonstrated survival benefit and a delay in the appearance of skeletal events in PCRC.

At present, the role of radiopharmaceuticals, at the expense of determining which patients could benefit from treatment with radium-223 and when, should be limited to extensive painful bone metastases.

**External radiotherapy**

Radiotherapy in bone metastases leads to a decrease in pain and in analgesic consumption, functional improvement and to a reduced risk of fractures in load-bearing bones. When pain is limited to one or limited locations, local-field radiotherapy can achieve pain relief in 80–90% of patients with a complete response in 50–60%. Multiple randomized trials have compared fractionated treatment with single-session schemes. The ASTRO guidelines identify similar symptomatic relief and a better cost-effectiveness ratio with a single 8-mg dose when compared to fractionated schemes.

Early treatment is advisable in cases of moderate or severe pain by using hypofractionated schemes in one single session.

**Analgesics**

Pharmacological management in the treatment of painful bone metastases follows the WHO recommendations on
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Progressive staggering with a first stage including paracetamol, AAS and non-steroidal anti-inflammatory (NSA) drugs, a second stage including minor opiates (codeine, tramadol), either associated with NSA drugs or not, and a third stage which may involve major opiates (morphine, fentanyl), but generally with non-opioid drugs.

Surgery

Its objectives are pain alleviation and functional preservation or restoration. Multiple procedures have been described to manage chronic nociceptive and neuropathic pain, resolve or prevent pathological fractures, as well as spinal cord compression, a complication causing pain and a potentially irreversible loss of neurological functions. These procedures include from minimally invasive techniques such as radiofrequency, cryotherapy or vertebroplasties to more complex exeresis surgeries. Decompressive and stabilization surgery, followed by radiotherapy, remains as the main indication for patients with unstable pathological fractures, a limited tumor burden and a favorable prognosis.\textsuperscript{37}

Conclusion

The prevention and management of bone involvement in patients with PCa is a demanding challenge that requires an individualized approach. In those patients where starting prolonged AST is considered, it is compulsory to determine the basal risk of the bone in order to introduce, along with general prevention measures, antiresorptive therapies in those patients with a high risk of developing fractures. The treatment of a metastatic patient must be multidisciplinary and early consider the onset of treatments reducing the risk of skeletal events, along with hormone-based or chemotherapeutic treatments.
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Conflict of interest

The authors declare that they have no conflict of interest.

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