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Importance of bone assessment and prevention of osteoporotic fracture in patients with prostate cancer in the gonadotropic hormone analogues use

Importância da avaliação óssea e da prevenção da fratura osteoporótica em pacientes com câncer de proìstata em uso de anaìlogos do hormônio gonadotrófico

Bruno Lopes Cançado[1]; Luiz Carlos Miranda[2]; Miguel Madeira[3]; Maria Lucia Fleiuss Farias[3]

A B S T R A C T

The antiandrogenic therapy (ADT) for prostate cancer represents an additional risk factor for the development of osteoporosis and fragility fractures. Still, bone health of patients on ADT is often not evaluated. After literature research we found that simple preventive measures can prevent bone loss in these patients, resulting in more cost-effective solutions to the public health system and family when compared to the treatment of fractures.

Key words: Prostatic Neoplasms. Osteoporosis. Hormones. Gonadotropin Releasing Hormone/analogues & derivatives. Testosterone/antagonists & inhibitors.

INTRODUCTION

Prostate cancer (PCa) has its highest incidence among men 50-70 years of age[1]. There are several available methods for treatment of patients with PCa, such as active surveillance, resection, radiotherapy and androgen deprivation. Gonadotropin-releasing hormone analogs (GnRHa) may be indicated as adjunctive therapy in the treatment of metastases or as the therapy of choice in biochemical recurrence of primary disease[2].

From the age of 40 on, there is deterioration in bone health. Maternal family history of osteoporosis, smoking, diabetes mellitus, alcoholism and drug use increase the risk of developing osteoporosis[3-5]. Although the risk to bone health is recognized, usually patients using GnRHaare not evaluated for osteoporosis. Often the bone mineral density (BMD) before the start of antiandrogenic therapy (ADT) is not performed, and in many cases, analysis of bone health is performed only after a major adverse outcome (fracture) has occurred[6-11].

Fractures cause a significant increase in morbidity and mortality of patients during the first year after its occurrence. Its cost to the public health system is much higher than a proper investigation associated with the treatment of osteoporosis in patients with ADT. The psychosocial cost is also high for the patient's family, because patients with fractures require more intensive care, with frequent visits to the doctor, physical therapy and home assistance to perform daily activities[12,13].

The relevance of this review is to arouse attention to the research and monitoring of bone health in patients with PCa undergoing ADT, contributing to the improvement in their treatment and monitoring.

Bone health and sex hormones

Until puberty, there is no difference between genders as to skeletal growth. Since then, the influence of hormones becomes larger and promotes in man a greater periosteal apposition, characterized by longer bones, of more external and internal perimeter and greater volume of cortical bone compared with women. Therefore, in adulthood, men have a higher bone mass (larger bone), bone mineral density being higher, although the bulk density does not differ between genders[3,14].

The distinct pattern of structural modeling and bone tissue increase between men and women is related to different hormone concentrations: basically higher testosterone levels in males. Testosterone is normally metabolizedto estrogen (17β-estradiol) by the aromatase enzyme found in adipose tissue and bone.

1. Postgraduate Program in Endocrinology, Universidade Federal do Rio de Janeiro, Rio de Janeiro State, Brazil; 2. Urology Service of the Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro State, Brazil; 3. Departament of Endocrinology, Faculty of Medicine, Universidade Federal do Rio de Janeiro, Rio de Janeiro State, Brazil.

Bone cells express three types of steroid receptors: one androgen (AR) and two estrogen (ERα and ERβ). Several studies suggest that most of the effects of testosterone on bone cells is mediated by aromatization, allowing their binding to estrogen receptors and subsequent synthesis of mRNA and production of proteins necessary for the formation and resorption of the bone matrix[3,13-15]. It is believed that the hormones produced in the testis might influence bone metabolism by other mechanisms. A recent study suggests that there is intense communication between the testicle and the bone, mediated by various routes, such as insulin-like growth factor 3 (IGF-3), endogenous synthesis of vitamin D and calcitonin for the production of bone cells. However, more information is needed to confirm these hypotheses[16].

In addition to the accumulation of bone mass in menbeing greater than in women, bone loss rate of the former is slower over aging. This is because the decrease in the rates of sex hormones in man are more gradual than in women[3,14-17]. From the age of 40 on, there is gradual replacement of skeletal muscle tissue with fat. In the bone there is a decrease in bone density at a rate of 0.5-1% per year[3,14,17-19]. A study in men between 50 and 100 years old confirmed the role of the decline in bioavailable free testosterone and in the loss of bone mass during aging[19].

It is estimated that, in the male population of the United States over 65 years of age, approximately 1.5 million will develop osteoporosis. In many cases, this will occur in association with one or more hazardous conditions, i.e., alcoholism, diabetes, vitamin deficiency, chronic use of corticosteroids, GnRH analogues etc[20-22]. In Brazil, two studies were carried out on the prevalence of fragility fractures in the general population. Both evaluated individuals over the age of 40 years and their results concur with theinternational ones. The first[18] evaluated 325 men living in the city of São Paulo and observed osteoporosis in 15.4%, diagnoses by bonedensitometry or fracture. The second was nationwide and was published in two parts[23,24]. In it were evaluated 725 men with a mean age 58.4 ± 12.8 years and the prevalence of fractures was 12.8%.

The standards for diagnosis of osteoporosis / osteopenia used in most studies have been based on female values[6,7,10,21,23-28]. Some authors have questioned whether the use of these measured parameters in the female population could not be underestimating the incidence of bone disease in men[14]. For them, if the diagnostic criteria were adjusted for gender, the incidence of bone disease in humans could have a 13% increase[3].

Prostate Cancer

Prostate cancer (PCa) is the second leading cause of death from cancer and the most common cancer in men in the United States and Brazil. In 2010, its incidence was greater than 196,000 new cases[29]. An estimated 8,500 patients have the disease in locally advanced or advanced stages at diagnosis, which makes them eligible for antiandrogenic therapy[29].

In Brazil, in 2010, the National Institute of Câncer(INCA) estimated the average age of diagnosis of PCa in 65 years[1]. The estimated incidence of new cases was 52,350 and in the same year, 26,600 deaths had PCa as their main etiology[1]. In the estimate published for the year 2014, the overall incidence increased to 68,800 new cases[28].

Even after successful initial treatment with external beam radiotherapy, brachytherapy or resection, nearly 40% of patients with locally advanced PCa will display biochemical recurrence at any time, that is, increase in the total PSA (PSAT)[30].

The role of hormones in the promotion and development of cancer was discovered in 1941 by Huggins and Hodges. His studies identified the affinity of prostate cells by testosterone, which resulted in Huggins being contemplatedwith the Nobel Prize for Medicine and Physiology in 1966. Since then, drugs that antagonize the action of testosterone have been used in the treatment of PCa[31,32].

Therapies based on the use of estrogens have been the treatment of choice for prostatic cancer in the past, but side effects in other systems, such as increase in cardiovascular and thromboembolic events, led to the search for new drugs[20,21]. Currently, the antiandrogenic drugs most commonly prescribed for the PCa are the GnRHa[2,33-35].

Pharmacology

The gonadotropin hormone (GnRH) is a peptide synthesized in the hypothalamus in the pre-optic core. After synthesis, GnRH is transported via vesicles through the axons to the anterior pituitary gland. In the pituitary gland, GnRH stimulates the production and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH).

The GnRHa act by binding to receptors on the pituitary gland in a reversible way. Initially, GnRHa stimulate the secretion of gonadotropic hormones, leading to transient paradoxical increase of this hormone in the bloodstream, which increases the concentration of testosterone (flare effect)[36]. Due to this feature, GnRHais usedalong peripheral androgen inhibitors in the early treatment, preventing the advancement of cancer[36,37]. However, after three weeks of saturation of pituitary receptors, secretion of testosterone reaches levels seen in surgically castrated patients[37].

Clinical effects

The ADT hormonal changes the male pattern from eugonadism for hypogonadism in a short period (usually between 30 and 90 days). This abrupt change in androgen concentrations leads patients to complain of symptoms of acute hormonal deficiency, such as hot flashes, emotional lability, headache, fluid retention and nausea. In the long term, patients may develop gynecomastia, weight gain, decreased libido, bone loss and fractures[7,8,10,13,25,31,35,37,38].

Antiandrogenic therapy, bone loss and fractures

The age range of patients with prostate cancer is in itself a risk factor for bone disease[7,8,10,20-23]. In Brazil, the average estimated age for the diagnosis of PCa is 65 years[1,28].

After ADT initiation, bone loss occurs more intensely in the first 24 months, reaching apeak rate of 4-6% per year. After this initial period, the rate of bone loss decreases, remaining constant at 2% per year[7,9,15,20,21,38]. Even so, the loss of 2% annual bone mass is higher than the physiological loss by natural aging, ranging from 0.5 to 1% per year[19,22,27].

The literature shows that approximately 5% to 10% of patients in ADTregimen will present with fractures after two years of treatment. The risk increases with therapy time[2,13,38-40]. Other studies confirm the presence of bone disease after a long period of ADT, with prevalence of 31% and 51% for osteoporosis and osteopenia, respectively, in patients with a treatment period of less than ten years[38].

Intermittent use of GnRHa did not show any protective effect on the loss of bone density compared with continuous ADT[9,27,38]. In a study where patients had undetectable PSAT levels and had received the internationally recommended dietary supplementation of calcium and vitamin D, complete recovery of bone mineral density (BMD) at the pre ADT levels was not achieved even after a year of discontinuation of medication. The use of GnRHa further increases the risk of fractures[3,6,8,10,12,13,15,20-22,25,31,33,38,39].

COMMENTS

Despite the many literature data, an assessment of bone health is still usually neglected in ADT patients. Studies show that most doctors who work directly in the treatment of prostate cancer (urologists and / or oncologists) do not question their patients about bone symptoms[40].

In 2013, the National Osteoporosis Foundation (NOF) updated its protocol for patients at risk of developing osteoporosis[22]. It recommends that all patients above 50 years of age, before starting treatment with medications that can cause bone loss, be subjected to an assessment of their bone mineral density (BMD) by bone densitometry (DXA)[4,7,8,10,22,26,27].

There is no consensus on how to treat bone loss induced by the use of GnRHa and other medications. The literature seems to agree that exercise (aerobic and anaerobic load), sun exposure and appropriate dietary supplementation with calcium and vitamin D can reduce it, but not preventit[6-8,10,27].

Vitamin D deficiency is very common in the elderly, especially in the osteoporotic population. Studies in countries where sun exposure is more constant throughout the year (South and Central America, Africa and Middle East), have shown that vitamin D levels do not usually vary much according to the seasons and in more extreme latitudes countries (North America, Europe, Northern Asia)[3,14].

Although Brazil is a tropical country, national studies show that our people may experience a deficiency of vitamin D. In São Paulo researchers found that the late winter vitamin D rates were lower when comparedwith late summer ones in the studiedsubjects[41].

The aGnRHs are not the only drugs that induce osteoporosis[3,4,14]. Drugs such as glucocorticoids, aromatase inhibitors, proton pump inhibitors, thiazide diuretics, deposit contraceptives, unfractionated heparin, among others, also have deleterious effects recognized in bone health. The Brazilian Society of Rheumatology suggests that the cutoff points for the treatment and prevention of osteoporosis in male patients on corticosteroid therapy regimen for more than three months are, respectively, -1.8 DP and -1.0 DP[42]. Another study suggests that patients using aromatase inhibitors also have cut-off points for initiation of treatment reduced for -1.5 DP[3,16].

Although the reviewed literature does not provide enough data for this comparison, patients using GnRHa also feature a large bone loss, markedly in the first 24 months[2,13,38,40]. So maybe comparative studies were to be conducted to verify that,in patients using GnRHa, the cutoff levels for bone disease treatment initiation should be diminished, as suggested in patients taking aromatase inhibitors and corticosteroids.

RECOMMENDATIONS

Patients taking medications associated with bone loss must perform densitometry prior to treatment start. Those with normal bone mineral density (BMD) and low risk of developing osteoporosis should receive only nutritional supplementation, in order to reach 1200 mg / day of elemental calcium and 800 to 1000 IU / day of vitamin D, accompanied by physical activity. The monitoring of BMD and bone densitometry should be annual when in the presence of these drugs[4,6-8,10,22,27,42,43]. Patients with moderate to high risk (osteopenia / pre-ADT osteoporosis) who have been submitted to measuresfor patients with low risk, should undergo more aggressive treatment with bisphosphonates[4,6-8,10,22,27,32,42]. Injectable bisphosphonates appear to be more effective in preserving bone mass loss when compared with the oral ones[2,8-10,34,36,37]. The best results were achieved with the use of injectable zolendronic acid, even when performed in a single annual dose of 5 mg[8,36]. The denosumab (Dmab), a powerful anti-reabsortion drug,was recently approved for treatment of men with non-metastatic prostate cancer in ADT. Patients who received 60mg subcutaneous. Dmab vs placebo, every six months, obtained reduction in the incidence of vertebral fractures anddisplayedincreased BMD to 62% after 36 months[44].

The cost of fracture prophylaxis is significantly lower than the hospital costs of a fracture episode[4,13,36]. In

2001, it was estimated that a hip fracture cost about 12,000 pounds to the UK health system, while a year of therapy with bisphosphonates, which reduces the risk of fracture by 50%, cost 335 pounds / year[13]. In Brazil, it was estimated that the cost of a hospital osteoporotic hip fracture in the Supplementary Health System reaches R$ 24,000.00[45].

FINAL CONSIDERATIONS

Bone loss associated with antiandrogenictherapy in patients with prostate cancer is underestimated by physicians around the world. The economic and social costs for the treatment of osteoporotic fractures are high. After hospital discharge, patients often need physical therapy to help them return to their normal activities. In some cases, full recovery is never reached, and affected individuals will need assistance to enable them to perform their daily activities for the rest of their lives. The adoption of measures to avoid the appearance of fractures should be encouraged due to their benefits to affected individuals and their families, and the high costs that a fragility fracture imposes to the health system in general.

R E S U M O

A terapia antiandrogênica (TAD) para câncer de próstata representa um fator de risco adicional para o desenvolvimento de osteoporose e fraturas de fragilidade. Mesmo assim, a saúde óssea dos pacientes sob TAD frequentemente não é avaliada. Após pesquisa na literatura, observamos que medidas preventivas simples podem prevenir a perda de massa óssea nestes pacientes, resultando em soluções mais custo-efetivas para o Sistema Público de Saúde e familiares quando comparadas ao tratamento das fraturas.

Descritores*: Neoplasia da Próstata. Hormônios. Osteoporose. Hormônio Liberador de Gonadotropina/análagos & derivados. Testosterona/antagonistas & inibidores.*

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Address for correspondence:
Bruno Lopes Cançado
E-mail: blc1904@hotmail.com