

## Research Article

# Bone Mineral Density in Prostate Cancer Patients with Drug Induced Hypogonadism

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## Low T or True Male Hypogonadism

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### Abstract

Bone loss in patients with prostate cancer undergoing anti-androgen therapy is underestimated by physicians. Osteoporosis is a silent condition that can lead to major fracture events. The osteoporosis's fractures has as consequence a decrease in a patient's general health and quality of life, an increase in morbidity and mortality, and an increase in the cost to the health care system. The application of preventive measures to avoid osteoporosis results in a simpler and more cost-effective solution, with few drawbacks to the patient, compared with the cost of treatment for osteoporosis-related fractures.

## INTRODUCTION

Male hypogonadism has numerous and diverse causes, including genetic abnormalities, systemic diseases, hypopituitarism, and induction by drugs. In this review, we focus on drug-induced hypogonadism and its skeletal effects in patients treated with gonadotropin-releasing hormone (GnRH) inhibitors for locally advanced or advanced prostate cancer. It is important to emphasize that the negative effects of GnRH-induced hypogonadism on bone are often underestimated by physicians and are frequently underdiagnosed [1-18].

## PROSTATE CANCER

Prostate cancer is the most common cancer and the second leading cause of death from cancer in men in the United States (US). In 2010, the incidence of prostate cancer in the US was over 196,000 cases, leading to more than 28,000 deaths that year [19]. An estimated 8,500 patients have locally advanced or advanced disease at the time of diagnosis and, therefore, are eligible for anti-androgen therapy [19]. Furthermore, despite undergoing mono therapy for prostate cancer (surgery, external beam radiotherapy, or brachytherapy), almost 40% of patients with an initial diagnosis of locally advanced prostate cancer will develop prostate-specific antigen (PSA) recurrent disease (i.e., progressively increasing PSA). At this point, patients will be eligible for adjuvant treatment, such as radiotherapy and/or GnRH antagonist treatment, to control the disease [19].

The role of hormones in the promotion and development of cancer was discovered in 1941 when Huggins and Hodges described the hormonal affinity of prostate cancer cells [20,21]. Based on this discovery, Huggins was awarded the 1966

Physiology of Medicine Nobel Prize. Since then, drugs that antagonize the action of testosterone have been used in the treatment of prostate cancer [23,24].

In the past, an estrogen-based therapy was the first choice of treatment for prostate cancer. Although this type of therapy yielded no negative side effects on bone, reports of a high incidence of cardiovascular and thromboembolic events motivated the search for new therapies [3-8,11,13,25,26]. Currently, the most prescribed anti-androgen drugs for prostate cancer are GnRH inhibitors such as goserelin, leuporelin, and triptorelin [1-18,25-40].

## PHARMACOLOGY

GnRH is a peptide hormone that is synthesized in the pre-optic nucleus of the hypothalamus and is transported via vesicles to the anterior pituitary along the axons. In the pituitary gland, GnRH stimulates the production and release of luteinizing hormone (LH) and follicle-stimulating hormone (FSH). The secretion of GnRH is pulsatile, with low-frequency pulses favoring FSH release and high-frequency pulses favoring LH release. This hormonal pulsatile release pattern avoids the down regulation of the membrane receptor proteins of the target cells and maintains the release of these hormones within the normal range.

GnRH inhibitors (GnRHi) bind to GnRH receptors in the pituitary gland in a reversible manner. Initially, GnRHi stimulate gonadotropin release and lead to a paradoxical rise in serum testosterone levels (flare effect); however, after three weeks, the saturation of these receptors induces a decrease in testosterone to levels observed with castration (down regulation). Because of the flare effect, an anti-androgen drug is usually administered

along with peripheral competitive androgens blockers (e.g. ciproterone) in the first month of treatment [1-18,24-27,31,32,38-40].

## CLINICAL EFFECTS

After starting anti-androgen therapy (ADT) for prostate cancer, hormone levels fall to those observed with castration within three months. This effect leads patients to report symptoms of acute hormonal deficiency (hot flushes, emotional instability, headaches, fluid retention, and nausea). Long-term side effects are related to treatment duration and can include gynecomastia, alterations in body hair distribution, weight gain, decreased libido, bone loss, and fractures [1-18,24-27,31,32,38-40].

### Sex steroids and bone health

The skeleton grows and changes its shape in childhood and adolescence by bone modeling. After peak bone mass is reached by approximately 30 years of age, the integrity of the skeleton depends on the renewal of bone, a process known as bone remodeling or bone turnover. This process is under the influence of hormones, such as parathyroid hormone and vitamin D (both of which are linked to calcium and phosphorus homeostasis), in addition to growth hormone, insulin-like growth factor 1, thyroid hormone, and sex steroids. Diet, exercise, sunlight exposure, weight, and certain diseases (e.g., thyroid dysfunction, hypercortisolism, and parathyroid diseases) also have a significant influence on bone homeostasis [6,8,10-13,15-18,26-30].

Bone cells express both androgen receptors (ARs) and estrogen receptors (ER $\alpha$  and ER $\beta$ ). The major action of testosterone on bone cells, however, occurs after it is aromatized by the p450 19A1 enzyme aromatase. The resulting hormone, 17 $\beta$ -estradiol, then binds to ER $\alpha$  and ER $\beta$  and promotes mRNA transcription, which induces the production of proteins necessary to form bone matrix [28-30]. Therefore, estrogen stimulates bone formation and subsequently increases bone density and strength.

Estrogen deficiency in postmenopausal women is the main contributor to bone porosity and increased risk for fragility fractures [28-30]. In aging men, the decline in the sex steroids testosterone and estradiol significantly contributes to bone loss and fractures [35]. The testis can also affect bone homeostasis by other pathways. A recent study suggests the existence of an intense crosstalk between the testis and bone. The influence of the testis on bone metabolism appears to be mediated by substances such as insulin-like factor-3 (ILF-3), endogenous vitamin D synthesis, and the production of calcitonin by bone cells [30].

### Aging and osteoporosis in men

Bone acquisition during adolescence is greater in men than in women. Additionally, because the decrease in sex steroids with age in men is not as sudden and intense as it is in women, bone loss and osteoporotic fractures occur later in males [28-30,33,34].

Sex steroids are found in the bloodstream as both free hormones and hormones bound to carrier proteins, with the main carrier protein being sex hormone-binding globulin (SHBG). The

synthesis of SHBG in the liver increases with age, which leads to a further decline in free testosterone (an active hormone) in plasma [34]. Consequently, at approximately 60 years of age, men have an increase in the proportion of fat to muscle tissue, while bone mineral density (BMD) decreases at a rate of 0.5-1% per year [1-18,24-27,31,32,38-40].

In the US, at 65 years of age, nearly 3.5 million men will be at risk for the development of bone disease and 1.5 million will develop osteoporosis due to factors such as alcoholism, diabetes, vitamin deficiency, or chronic use of corticotherapy [2,3,6,10,12,31,32,40].

The osteoporotic and osteopenic states are usually oligosymptomatic or asymptomatic. These states normally present with a major event such as a fragility fracture at a particular skeletal site (e.g., hip or spine), resulting in a major health problem. In the US, 33% of osteoporotic-related hip fractures occur in male patients [2,3,6,10,12,31,32,40]. Men with hip fractures have a longer hospitalization and a 20% higher risk of mortality compared with women in the same physical condition [2,3,6,10,12,31,32,40].

The costs of osteoporotic fractures are overwhelming. After discharge from the hospital, patients usually need physiotherapy to help them return to their normal activities. In some cases, they never achieve a full recovery and will need assistance to help them in their daily activities for the rest of their life [2,3,6,10,12,31-33,40].

### BMD measurement and classification of strength

BMD is usually measured by dual-energy X-ray absorptiometry (DXA). According to the International Society for Clinical Densitometry 2013 guidelines, DXA measurement of the hip, spine, or proximal third of the radius can confirm the diagnosis of osteoporosis, predict future fracture risk, and monitor patients by the performance of serial assessments. Areal BMD is expressed in absolute terms as grams of mineral per square centimeter scanned (g/cm<sup>2</sup>) and can also be expressed relative to the BMD of either an age-, gender-, and ethnicity-matched reference population (Z-score) or a young-adult reference population of the same gender (T-score). The difference between a patient's BMD and the mean BMD of the reference population, divided by the standard deviation (SD) of the reference population, is used to calculate the T-score and Z-score. The criteria for classification as osteopenia (T-score between -2.5 and -1 SD) and osteoporosis (T-score at or below -2.5 SD) are recommended for postmenopausal women and men 50 years of age and older [7,26,32,33,38,39].

However, bone fragility is not solely associated with bone mineral density; it is also associated with the deterioration of bone micro architecture characteristic of osteoporosis. An increased bone turnover, leading to disruption of the trabecular network and increased porosity of cortical bone, negatively affects bone health. While these alterations occur with aging [41], a faster and more intense bone loss is observed with certain drugs that affect bone. These alterations in bone microarchitecture most likely explain fragility fractures in patients classified as having "osteopenia" or even "normal bone density" by DXA [42,43].

### ADT AND BONE LOSS

ADT shifts the hormonal decline in men from a state of

eugonadism to hypogonadism in a relatively short period of time (usually 30 days), and, as expected, the body reacts strongly to this abrupt change [1-18,24-27,31,32,35,38-40]. The prevalence of osteopenia and osteoporosis in the prostate cancer population is not known, but the consequences of ADT-induced bone loss can be assessed within the first 9 months after the initiation of ADT [1-18,24-27,31,32,35,38-40]. Bone loss is more intense during the first twenty-four months of therapy, reaching a rate of 4-6% per year. After these first two years, the rate of bone loss drops to a constant rate of approximately 2% per year, which is still higher than the normal rate of bone loss (0.5-1%) [18,24-27,31,32,35,38-40]. The literature shows that nearly 5% of patients present fractures event after 2 years of ADT (3-31), and this percentage increases with therapy duration.

However, the cessation of ADT does not guarantee the recovery of bone to the previous status. Intermittent use of GnRHi may not spare patients from bone loss and the complications observed with continuous ADT [2-4,7,8,24,32,39]. In one study, a full recovery of bone to pre-treatment levels one year after ADT interruption was not achieved in all patients who had received intermittent ADT for 2 years, even though PSA levels were undetectable and the patients received calcium and vitamin D supplementation [24]. Other studies confirmed bone disease after long-term ADT, with rates of 30% and 51% for osteoporosis and osteopenia, respectively, after a 10-year or longer period of treatment [2,7,10-13,26,33,35,36].

### Specific approach to bone loss in patients undergoing adt

Despite these data, bone health is usually neglected in patients undergoing ADT. Studies show that the majority of doctors who work directly in the management of prostate cancer (i.e., urologists and oncologists) do not ask their patients about bone symptoms, even when the patients have any bone symptoms complaints [40].

In 2013, the National Osteoporosis Foundation (NOF) published an update of guidelines (initially published in 2008) to help physicians manage patients at risk for osteoporosis [34]. The NOF recommends that all patients over 50 years of age who are candidates for ADT (or other medications associated with bone loss) should undergo DXA scanning to assess BMD before starting treatment, with repeated exams after one year and then every two years or as needed (e.g., after fractures) [34].

There is no consensus concerning how to treat GnRHi-induced bone loss. The literature indicates that exercising (weight-bearing and aerobic exercises), adequate sunlight exposure, and calcium and vitamin D supplementation can reduce bone loss but do not prevent it [6,8,40,10-17,25-27,33,35-37,40].

In otherwise healthy men with prostate cancer who will be starting ADT therapy (especially those with a normal BMD and a low risk for developing osteoporosis), the recommendation is to guide lifestyle changes and to prescribe calcium (1200 mg daily) and vitamin D (800-1,000 IU daily) supplements to support the diet. The patients should then be followed with DXA once a year while ADT is maintained [6,8,40,10-17,25-27,33-37,40].

Patients at a moderate or high risk for fractures (osteopenia or osteoporosis based on DXA results) when ADT therapy is started or who are already undergoing ADT require more aggressive

management using bisphosphonates or other bone-protective drugs. The use of injectable bisphosphonates produces better results compared with oral bisphosphonates [6,8,40,10-17,25-27,33,35-37,40]. The literature shows very good outcomes with injectable pamidronic acid, but the best results associated with ADT-induced bone loss are achieved with zoledronic acid, using the same 5 mg annual dose that is employed for other causes of osteoporosis [10-17,26-27,33,35-37,40].

The costs of using bisphosphonates are significantly lower than the costs of hospital care. Peters et al. estimated that a hip fracture costs up to 12,000 pounds in the UK, while one year of bisphosphonate therapy, which reduces the fracture risk by 50%, costs to the health care system 335 pounds [32].

### CONCLUSION

In conclusion, the bone loss associated with ADT is underestimated by physicians. Osteoporosis is a silent condition and usually manifests with major fracture events. These fractures lead to serious risks to patients' health, increase morbidity and mortality, and increase the cost to the health care system. Preventive measures can be applied with few drawbacks to the individuals. Preventive measures are simpler and less expensive compared with the treatment of osteoporosis-related fractures.

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