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# Bone health and its correlates in Korean prostate cancer patients receiving androgen deprivation therapy

Soo Hyun Kim [a, *], Do Hwan Seong [b], Sang Min Yoon [b], Young Deuk Choi [c], Youngkyu Song [d], Hosook Song [e], Eunju Choi [a]

[a] Department of Nursing, Inha University, Incheon, South Korea
[b] Department of Urology, Inha University Hospital and College of Medicine, Inha University, Incheon, South Korea
[c] Department of Urology, Clinical Trials Center for Medical Devices, Yonsei University College of Medicine, Seoul, South Korea
[d] Graduate School, Catholic University, Seoul, South Korea
[e] Department of Urology, Inha University Hospital, Incheon; College of Nursing, Ajou University, Suwon, South Korea

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ABSTRACT

*Purpose:* This study aimed to examine bone health status, identify factors associated with bone mineral density (BMD), and determine potential risk factors for osteoporosis in Korean prostate cancer patients receiving androgen deprivation therapy (ADT).

*Methods:* Using a cross-sectional descriptive design, we recruited 139 men with prostate cancer receiving ADT at two university-based hospitals in South Korea. Participants completed a self-reported questionnaire and underwent dual energy X-ray absorptiometry testing. BMD ($gm/cm^2$), bone health status (normal BMD, osteopenia, and osteoporosis), and lifestyle variables (physical activity, smoking, and alcohol consumption) were measured.

*Results:* The prevalence in our sample was 49.6% for osteopenia and 17.3% for osteoporosis. In multivariate linear regression analyses, BMD was positively associated with body mass index, number of comorbidities, and level of physical activity and negatively associated with being unemployed or retired, having a lower monthly income, and being treated with gonadotropin-releasing hormone therapy alone. In logistic regression analyses, potential risk factors for osteoporosis were low monthly income (OR = 4.33, $p = 0.011$), receipt of radiation therapy (OR = 4.69, $p = 0.018$), and lack of regular physical activity (OR = 2.63, $p = 0.035$).

*Conclusions:* Our results suggest that a proportion of prostate cancer survivors who are receiving ADT warrant monitoring to prevent osteoporosis, particularly men of lower economic status and those having lower levels of physical activity. Nurses can play an important role in screening these high risk groups.


## 1. Introduction

Prostate cancer is the world's fourth most common cancer and the second most common cancer for men, with more than a million new cases diagnosed in 2012 (15% of male cancers and 8% of the total) (Ferlay et al., 2013). In Korea, prostate cancer is the fifth most common malignancy in men (Korea Central Cancer Registry, 2014), and although the incidence is lower in Korea than in western countries, it is increasing at an annual growth rate of 12.7% (Korea Central Cancer Registry, 2014). Minimizing the morbidity and mortality associated with prostate cancer is at the forefront of care for this population (Koo et al., 2015).

Patients with clinically localized prostate cancer are usually treated with radical prostatectomy or radiation therapy, but androgen deprivation therapy (ADT) is commonly used in cases of metastatic disease or biochemically recurrent prostate cancer. ADT involves hypogonadism induction through orchiectomy, gonadotropin-releasing hormone (GnRH) agonists alone, or combined androgen blockade (Heidenreich et al., 2014). Men with biochemically recurrent disease alone may live for many years and experience long-term exposure to ADT (Heidenreich et al., 2014; Loblaw et al., 2007). That may lead to significant adverse effects, one of which is bone loss (Eastham, 2007; Schwandt and Garcia, 2009; Stava et al., 2009).

* Corresponding author. Department of Nursing, Inha University, 100 Inharo, Nam-gu, Incheon, 22212, South Korea.
*E-mail address:* soohyun@inha.ac.kr (S.H. Kim).

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ADT reduces oestrogen levels in men by blocking the production of androgens (e.g. testosterone), which are precursors for oestrogen biosynthesis via aromatase (Guise et al., 2007). Thus, ADT reduces bone mineral density (BMD), which increases the risk of osteoporosis and skeletal fractures (Morote et al., 2007; Shahinian et al., 2005; Smith et al., 2005). While cancer-free elderly men lose an average of 0.5–1% of their BMD annually, the rate in men receiving ADT can be as high as 4.8% (Alibhai et al., 2013; Greenspan et al., 2005; Higano et al., 2004; Morote et al., 2006; Smith et al., 2004; Yu et al., 2012). In their first year of ADT therapy, men have a 5- to 10-fold higher rate of bone loss, and the risk of fracture increases as the therapy continues (Greenspan et al., 2005; Shahinian et al., 2005). In a population-based case–control study (Abrahamsen et al., 2007), prostate cancer was associated with an increased risk of hip fracture (OR, 3.7; 95% CI, 3.1–4.4), and the prevalence increased with treatment duration. The overall fracture rate in men receiving ADT was 6%–20% after 1–4 years of treatment, 45% after 7 years, and 73% after 15 years (Guise et al., 2007). Since fracture at any location doubles the mortality risk in men receiving ADT for prostate cancer (Beebe-Dimmer et al., 2012; Limburg et al., 2014), prevention, early diagnosis, and treatment of cancer treatment-induced bone loss (CTIBL) are becoming important issues in such patients.

Clinical management of bone health has not been commensurate with the importance of prevention and treatment of CTIBL. A decade ago in a study of 184 patients on ADT, only 15% reported receiving any type of prevention information or therapy to maintain bone health (Tanvetyanon, 2005). In a more recent report, bone health assessment was not documented in 69% of patients on ADT (Dhanapal and Reeves, 2012). The threat of CTIBL in prostate cancer patients, however, requires that the healthcare team identify high-risk patients as early as possible (Kim et al., 2013; Limburg, 2007). Oncology nurses play an important role in identifying such patients, ensuring timely education, interventions, and referrals (Limburg et al., 2014).

While most research on bone health among this population has been conducted in western countries (Bruder et al., 2006; Chen et al., 2002; Morote et al., 2007; Morrison et al., 2011; Ryan et al., 2007; Wei et al., 1999), recent evidence suggests an ethnic variation in the effects of ADT on BMD. For example, Japanese men treated with ADT have low rates of osteoporosis (range, 8.6%–12.1%) (Wang et al., 2008; Yuasa et al., 2010), while Caucasian and African Caribbean men have high rates (range, 26.9%–42.9%) (Bruder et al., 2006; Morote et al., 2007; Morrison et al., 2011; Wei et al., 1999). Thus, there is a need to examine the impact of ADT in Korean men with prostate cancer, which can contribute to the development of an ethnically-sensitive programme for bone health promotion. Moreover, the numerous studies on the adverse effects of ADT on bone health have focused on identifying sociodemographic, disease-related, and treatment-related factors. While one study reported that calcium/vitamin D supplement use and alcohol use were positively associated with BMD, few studies have examined associations with lifestyle variables (Ryan et al., 2007). We therefore investigated bone health status and its correlates, including lifestyle variables as well as sociodemographic and clinical variables, in Korean prostate cancer patients receiving ADT.

## 2. Methods

### 2.1. Study design and participants

Participants for this cross-sectional study were recruited through the urology outpatient departments at two university-based hospitals in South Korea. Eligible participants were men older than 18 years who had been diagnosed with prostate cancer and were currently receiving ADT. Men who were non-Korean, had another cancer(s), a metastasis, concomitant bone metabolic disease (e.g., primary hyperparathyroidism, hypercalcemia, chronic hypercortisolism, renal failure, or Paget's disease), or were diagnosed with osteoporosis prior to the prostate cancer diagnosis were excluded. Of the 246 prostate cancer patients screened from May 2013 to September 2014, 85 were excluded (17 had other cancer(s), 51 had metastases, and 17 were diagnosed with osteoporosis before being diagnosed with prostate cancer). Among the remaining 161 men, 22 refused to participate in the study saying they were not interested ($n = 7$), had scheduling problems ($n = 9$), or felt too ill ($n = 6$), leaving 139 included in the final analysis.

### 2.2. Procedures

The study protocol and consent form were reviewed and approved by the Institutional Review Boards of the participating institutions. Research nurses identified potential participants through electronic medical record systems and met participants at a private room in the urology outpatient department and explained the study purpose. Each participant was provided with an informed consent form and a questionnaire was administered upon signed agreement to participate. A self-reported questionnaire gathered information on sociodemographics, comorbidity, and lifestyle behaviors. After completion of the questionnaire, participants were weighed wearing light clothes and no shoes, their height was measured, also without shoes, and they underwent dual energy X-ray absorptiometry (DXA) testing.

### 2.3. Measurements

#### 2.3.1. BMD

BMD was measured by DXA using a QDR-4500A apparatus (Hologic, Bedford, MA, USA) at lumbar spine, femur neck, and total hip, with results reported in gm/cm$^2$ at each site. BMD values also were reported as a T-score, which is the relevant measure when screening for osteoporosis. The T-score is the number of standard deviation (SD)s by which the subject measured bone mass deviates from the mean of a young normal population of the same sex at a given site (Higano, 2003). For example, T-score of −2.5 describes a bone density that is 2.5 SDs below the mean of a thirty-year-old. T-scores can be computed by DXA testing. According to World Health Organization (WHO) criteria, osteoporosis is defined as a T-score $\leq -2.5$, osteopenia as a T-score between −1.0 and − 2.5, and normal BMD as a T-score $\geq -1.0$ at any measured site (WHO, 2007).

#### 2.3.2. Sociodemographic and clinical factors

The sociodemographic factors we considered were age, marital status, education, employment status, monthly income, and body mass index (BMI). Comorbidity and all variables except BMI were collected by means of a self-reported questionnaire. BMI was calculated as body weight over height squared (Kg/m$^2$). Research nurses collected most clinical variables [tumor stage, Gleason score, prostate-specific antigen (PSA) level, type of treatment, type and duration of ADT treatment] from electronic medical records. The Gleason score, which is used to evaluate the prognosis of men with prostate cancer, is based on the microscopic appearance of prostate tissue from a biopsy (Epstein et al., 2005). Gleason scores range from 2 to 10, with 2 representing the most well-differentiated tumors and 10 the least-differentiated tumors. Prostate cancers with a Gleason score $\leq$6 are usually associated with rather good prognoses (Pierorazio et al., 2013). PSA is a protein produced by cells of the prostate gland. The concentration, which is usually reported as ng/mL blood, is often elevated in men with prostate cancer and is thus a good screening tool (National Cancer Institute, 2015).