Bone Mineral Density in Prostate Cancer: A Comparative Study of Patients With Prostate Cancer and Healthy Controls Using Propensity Score Matching

Taekmin Kwon, In Gab Jeong, Myungchan Park, Dalsan You, JungBok Lee, Hong Kyu Kim, Sungwoo Hong, Jun Hyuk Hong, Hanjong Ahn, and Choung-Soo Kim

OBJECTIVE To determine whether the prevalence of prostate cancer is associated with a decrease in bone mineral density (BMD) compared to a healthy control group and to identify the factors associated with osteoporosis in patients diagnosed with prostate cancer before the initiation of any kind of treatment.

MATERIALS AND METHODS A retrospective study was conducted in 582 patients with prostate cancer and 2536 healthy men. Confounding variables affecting BMD, including age, serum testosterone, body mass index (BMI), diabetes mellitus, hypertension, and smoking were matched in the 2 study groups using propensity score analysis.

RESULTS The propensity score model included 6 variables, and matching by propensity score yielded 502 patients in the prostate cancer group matched to 502 men in the healthy control group. On the basis of the lowest T-score available, a high prevalence of osteoporosis was found in the prostate cancer group ($P = .0001$). Prostate cancer was the factor correlating significantly with osteoporosis before propensity score matching (odds ratio [OR] 2.96, $P < .001$) and after propensity score matching (OR 3.22, $P < .001$). By multivariate analysis, conducted to assess the significance of each variable affecting the development of osteoporosis in patients with prostate cancer, bone metastasis was found to be an independent predictor of osteoporosis (OR 3.45, $P = .002$), along with BMI (continuous, OR 0.75, $P < .001$).

CONCLUSION After controlling for variables affecting BMD, prostate cancer was a risk factor for osteoporosis. Measurement of BMD is a logical first step in the clinical strategy to avoid or minimize potential bone-related complications in men with prostate cancer, especially if they have bone metastasis and a slender stature. UROLOGY 83: 385–392, 2014. © 2014 Elsevier Inc.

Prostate cancer is the most frequently diagnosed cancer other than skin cancer and is the second leading cause of death from cancer in men in the United States.[1] Most of these cases represent individuals with disease confined to the prostate; however, 20% of these men will be diagnosed with cancer that has metastasized either to locoregional lymph nodes or to bone and/or soft-tissue sites.[2] Androgen deprivation therapy (ADT) is the favored treatment for recurrent and/or metastatic disease, and a significant proportion of patients will undergo some form of hormone therapy.[3,4]

Unfortunately, ADT, although usually successful at controlling symptoms related to prostate cancer, may result in significant side effects. Short-term side effects, such as hot flashes and decreased libido, are most immediately troublesome to patients; long-term consequences of androgen deficiency include a potential decline in muscle mass and bone mineral density (BMD). Several studies have reported that ADT can induce bone loss and increase bone fracture risk in men with prostate cancer.[5,6] These results are of particular concern because osteoporosis and bone fractures negatively impact not only quality of life but also overall survival.[6,7] Thus, many studies have brought into focus the need to predict and prevent the progression of osteoporosis in patients with prostate cancer receiving ADT.[5,7,8] It has been recommended that all patients diagnosed with prostate cancer and initiating ADT

This trial was registered with Clinical Trials (AMC 2012-0408).

Financial Disclosure: *The authors declare that they have no relevant financial interests.*

From the Department of Urology, University of Ulsan College of Medicine, Asan Medical Center, Songpa-gu, Seoul, Korea; the Department of Clinical Epidemiology and Biostatistics, University of Ulsan College of Medicine, Asan Medical Center, Songpa-gu, Seoul, Korea; the Health Screening and Promotion Center, University of Ulsan College of Medicine, Asan Medical Center, Songpa-gu, Seoul, Korea; and the Department of Urology, University of Dankook College of Medicine, Cheonan, Korea

Reprint requests: Choung-Soo Kim, M.D., Ph.D., Department of Urology, University of Ulsan College of Medicine, Asan Medical Center, 388-1 Pungnap 2 dong, Songpa-gu, Seoul 138-736, Korea. E-mail: cskim@amc.seoul.kr

Submitted: May 18, 2013, accepted (with revisions): August 22, 2013

0090-4295/14/$36.00

http://dx.doi.org/10.1016/j.urology.2013.08.045

undergo baseline BMD measurements, and that repeat BMD assessments should be performed every 6-12 months in patients with baseline osteopenia or osteoporosis and every 1-2 years in patients with a normal baseline BMD.[8,9]

By contrast, a number of studies report a high prevalence of osteopenia and osteoporosis (ranging from 4%-75%) in patients with prostate cancer before receiving ADT and in those on watchful waiting.[9,10] To date, limited data are available on the risk factors for osteoporosis in men with prostate cancer before receiving ADT. Moreover, there are many factors, such as calcium intake, body mass index (BMI), lipid, and serum testosterone (TTT), that are correlated with osteoporosis.[11-13] Therefore, before initiating ADT in men with a diagnosis of prostate cancer, it is necessary to identify the causes of bone loss and to assess the risk factors for osteoporosis in a comparative study involving healthy men as controls.

The purpose of the present study was to determine whether the presence of prostate cancer is associated with a decrease in BMD compared to a healthy control group and to identify the factors associated with osteoporosis in patients diagnosed with prostate cancer before the initiation of any kind of treatments.

MATERIALS AND METHODS

Study Participants

The medical records of 582 patients diagnosed with prostate cancer were reviewed retrospectively. BMD was measured before treatment with radical prostatectomy, hormonal therapy, or radiotherapy in our institute between January 2006 and December 2011 (prostate cancer group).

The medical records of 2536 men of age 40 or older who visited the Health Screening and Promotion Center of the Asan Medical Center for a routine health checkup in 2009 were also reviewed (healthy control group). The health screening program included anthropometric measurements (height and weight), a blood test (complete blood cell count, basic chemistry, serologic test, blood coagulation test, thyroid function test, prostate-specific antigen [PSA], serum TTT, and assay for tumor markers), stool/urine analysis, abdominal ultrasonography, gastrofiberscopy, chest radiography, pulmonary function test, electrocardiography, BMD measurement, and a detailed clinical examination. All subjects were also asked to complete a questionnaire designed to assess sociodemographic factors, comorbidities, and current or past medications. The Institutional Review Board of the Asan Medical Center approved all procedures involved in the sampling and data collection, and written informed consent was obtained from all participants. Based on medical history and physical examination, patients with thyroid or parathyroid disease, uncontrolled diabetes mellitus (HbA1c $\geq$6.2%), cardiovascular disease, digestive disorders, and chronic steroid users were excluded.

Exposure Measures

The serum TTT levels were measured using a radioimmunoassay (Coat-A-Count total testosterone kit; Siemens, Los Angeles, CA). Blood samples for measuring serum TTT were collected between 08.00 and 11.00 a.m. to minimize daily variations in TTT level.[14] BMI was calculated using the formula: weight in kilograms divided by height in meters squared. The entire cohort was classified according to the World Health Organization BMI criteria into 4 groups: underweight (BMI $<$18.5 kg/m^2), normal weight (BMI 18.5-22.9 kg/m^2), overweight (BMI 23.0-24.9 kg/m^2), and obese (BMI $\geq$25.0 kg/m^2).[15] Lifestyle risk factors included smoking (current, past, or never). Personal history of specific medical conditions (eg, cancer, diabetes mellitus, thyroid or parathyroid disease, and hypertension, etc.) was assessed. Participants were asked to bring current prescription medications to the clinic visit. Specific classes of medications (eg, thiazide diuretics, oral corticosteroids, statins, or osteoporosis medications, etc.) were coded by trained staff using a computerized database. Bone metastasis was identified by x-ray analysis and bone scan.

Outcome Measures

BMD is considered to be the gold standard for diagnosing and assessing the severity of osteoporosis and the risk of fracture. For patients in the prostate cancer group, BMD was measured within 2-4 weeks after prostate cancer was diagnosed by biopsy and before any therapy was initiated. For healthy men in the control group, BMD and other variables were measured as part of routine health care at our Health Screening and Promotion Center. BMD was measured at baseline by dual energy x-ray absorptiometry of the lumbar spine and femur neck using a Delphi QDR (Hologic, Bedford, MA). BMD was expressed in standard deviation (SD) units relative to the BMDs of young adult men (T-score) and age-matched men (Z-score). Normal BMD was defined according to World Health Organization criteria as a T-score greater than -1 SD below the young adult mean value, osteopenia as a T-score between -1 and -2.5 SDs below that value, and osteoporosis as a T-score of -2.5 SD or lower below that value on the basis of the lowest T-score available.[16]

Statistical Analysis

Propensity score matching was performed to reduce treatment selection bias and potential confounding in this observational study and to adjust for significant differences in patient characteristics or lesions.[17] The propensity scores were estimated using a nonparsimonious multiple logistic regression model in both patients with prostate cancer and healthy subjects in this study. The following variables at the diagnosis for the patients with prostate cancer and at the medical examination for the non-cancer subjects were selected to calculate the propensity score to adjust discrepancy of baseline or general characteristics between the 2 groups: age, TTT, BMI, diabetes mellitus, hypertension, and smoking history. Matching 2 pairs was determined when the difference of predicted probabilities in healthy and prostate cancer groups was within $\pm$0.05. The discrimination and calibration ability of each propensity score model was assessed by means of the c statistic and the Hosmer-Lemeshow statistic. The goodness-of-fit statistic was 10.23 ($P = .25$) and the c statistic for the model was 0.92. For the development of propensity score-matched pairs without replacement (a 1:1 match), the local optimal algorithm with caliper method was used. Patients who did not have close pairs were not included in the final matched population. After matching the propensity scores of 582 patients (prostate cancer group) and 2536 men (healthy control group), 502 matched pairs were selected.

Continuous variables were expressed as means $\pm$ SD. Categorical variables were presented as numbers (%). Continuous variables were analyzed using the independent sample t test or