Journal of Bone and Mineral Metabolism (2019) 37:72–80
https://doi.org/10.1007/s00774-017-0897-5

ORIGINAL ARTICLE

Decrease of bone mineral density in Japanese patients with non-metastatic prostate cancer treated with androgen deprivation therapy

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Received: 8 October 2017 / Accepted: 14 December 2017 / Published online: 8 January 2018

Abstract

The aim of this study was to conduct a cross-sectional survey of investigations related to the bone mineral density (BMD) of both non-metastatic prostate cancer (NMPC) patients who have not yet received androgen deprivation therapy (ADT) and patients receiving prolonged ADT in Japan. Japanese male patients with NMPC who received continuous ADT or who were planning to receive ADT were enrolled in this study. Lumbar spine and femoral neck BMD was measured using dual-energy X-ray absorptiometry (DEXA). To assess patient characteristics, we searched medical records and questionnaires to determine whether they had any factors that could possibly affect BMD. A total of 230 patients with a mean age of 76.6 ± 6.4 years were evaluated. Of these, 151 (65.7%) were receiving ADT, and 79 (34.4%) had not yet received ADT. The mean duration of ADT was 37.4 ± 30.7 months. DEXA showed that as the duration of ADT increased, lumbar spine and femoral neck BMD decreased gradually ($p = 0.0005$ and $p = 0.0014$, respectively). Stepwise regression analyses revealed that the duration of ADT was a significant variable of both lumbar spine and femoral neck BMD. Moreover, as the duration of ADT increased, the prevalence of osteoporosis increased statistically ($p = 0.0002$). This study showed that ADT negatively affected lumbar spine and femoral neck BMD. It also showed a progressive increase in the prevalence of osteoporosis in Japanese NMPC patients with ADT.

Keywords Asian Continental Ancestry Group · Bone density · Gonadotropin-releasing hormone · Osteoporosis · Prostatic neoplasms

Introduction

Androgen deprivation therapy (ADT) is the standard treatment for recurrent, advanced, and metastatic prostate cancer. It is also frequently used in men with early stage disease to prevent cancer progression. In Japan, nearly half of patients with localized or locally advanced prostate cancer receive ADT without any other additional treatment [1]. Since it is possible for the duration of ADT to be prolonged in these conditions, associated long-term adverse effects should be taken into account by patients and physicians [2]. Osteoporosis has emerged as a clinically important adverse effect of ADT. Bone mineral density (BMD), a surrogate for fracture risk, decreases significantly during short-term and long-term treatment with ADT [3]. The annual loss of bone mass ranges from 2−8% at the lumbar spine and 1.8–4.1% at the femoral neck during ADT, which is five- to ten-fold higher than the 0.5–1.0% loss in the general population of aging men [4, 5]. ADT is associated with a significantly greater risk of clinical fractures [6, 7]. Clinical fractures during ADT correlate with shorter overall survival [8]. Decreased BMD and increased fracture risk in men receiving ADT are mostly reported from Western countries. The issue has not yet been investigated adequately in the Asian population. Therefore, we undertook a cross-sectional survey of investigations related to BMD of both non-metastatic prostate cancer (NMPC) patients who have not yet received ADT

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(hormone naive) and patients receiving prolonged ADT in Japan.

Materials and methods

Consecutive Japanese male patients with NMPC who attended our institution from January 2011 to November 2016 who were receiving continuous ADT or who were planning to receive ADT (hormone naive) were enrolled in this study. All of their prostate cancers had been proven pathologically by needle biopsy, and imaging tests (computed tomography, magnetic resonance imaging, and bone scintigraphy) revealed no metastatic lesions. ADT included gonadotropin-releasing hormone agonists (GnRHa) or combinations of GnRHa and anti-androgens. Patients receiving intermittent ADT and patients with castration-resistant prostate cancer were excluded. Moreover, patients with bone metabolic disease, including Paget's disease, osteomalacia, hyperprolactinemia, hyper- or hypothyroidism, hyperparathyroidism, and Cushing disease, or previous or concomitant treatment with bone-modifying agents, including bisphosphonates, denosumab, parathyroid hormones, selective estrogen receptor modulators, calcitonin, and calcitriol, were excluded from the study. The study protocol was approved by the local institutional review board.

BMD of the posteroanterior (PA) spine (L2–L4) and nondominant femoral neck was measured using dual-energy X-ray absorptiometry (DEXA). DEXA was performed using QDR-Discovery (Hologic, Inc., Marlborough, MA, USA). *T*-scores and young mean adult (YAM) values were calculated using the Hologic database for East Asian ethnicity. The coefficient of variation of BMD at our institution was 1.0% at both the PA spine and total hip. X-ray examinations of the PA spine and lateral spine (cervical, thoracic, lumbar) were performed to assess the presence of silent vertebral fractures. To assess patient characteristics, medical records and questionnaires were investigated to check whether they had any factors that possibly affected BMD such as body mass index (BMI), previous bone fractures of the spine or hip, any bone fractures during ADT, family history of bone fractures of the spine or hip, smoking status, alcohol excess, hypertension, diabetes, rheumatoid arthritis, chronic kidney disease (CKD) and steroid administration. Bone metabolism markers, bone alkaline phosphatase (BAP) as a bone formation marker, and urine type I collagen cross-linked N-telopeptide (urine NTx) or tartrate-resistant acid phosphatase 5b (TRACP-5b) as bone resorption markers were also measured to assess bone metabolism. Urine specimens for measuring urine NTx were obtained in the morning.

Baseline characteristics were compared using Student's *t* test, ANOVA, or Pearson's correlation analysis and Pearson's chi-squared test, respectively, for normally distributed continuous variables and for categorical variables. Stepwise regression analysis was used to find significant variables affecting BMD. Moreover, logistic regression analysis was performed to investigate significant variables influencing the diagnosis of osteoporosis. Statistical analyses were performed using StatView® 5.0 statistical software. Values were reported as the mean ± SD [median (IQR)] unless otherwise specified. All p values were two sided, and $p < 0.05$ was considered statistically significant.

Results

A total of 230 patients with NMPC were evaluated. Patient characteristics are summarized in Table 1. Of the 230 patients, 151 (65.7%) were receiving ADT, and 79 (34.4%) had not yet received ADT (hormone naive). The mean duration of ADT among the 151 patients who were receiving ADT was 37.4 ± 30.7 [median 31 (IQR 13.5, 52.5)] months. BMD was measured in 79 hormone-naive patients (34.4%), 63 patients (27.4%) who received <2 years of ADT, 47 patients (20.4%) who received from 2−4 years of ADT, 21 patients (9.1%) who received from 4−6 years of ADT, and 20 patients (8.7%) who received ≥6 years of ADT.

The results of DEXA are shown in Table 2. As the duration of ADT increased, lumbar spine BMD and femoral neck BMD decreased gradually ($p = 0.0005$ and $p = 0.0014$, respectively). Univariate analyses revealed that significant variables positively affecting lumbar spine BMD were diabetes and BMI; significant variables negatively affecting lumbar spine BMD were spinal fracture on radiography, duration of ADT, BAP, urine NTx, and TRACP-5b. Moreover, significant variables positively affecting femoral neck BMD were diabetes and BMI, and significant variables negatively affecting femoral neck BMD were age, spinal fracture on radiography, duration of ADT, BAP, urine NTx, and TRACP-5b (Table 3). On the other hand, any other factors of fracture—including previous bone fracture of the spine or hip, fracture during ADT, and family history of bone fracture of the spine or hip, and any other factors of lifestyle and lifestyle diseases including smoking status, alcohol intake, hypertension, CKD, and rheumatoid arthritis—were not associated with lumbar spine and femoral neck BMD.

We analyzed whether there was a relationship between BAP and the duration of ADT, between urine NTx and the duration of ADT, and between TRACP-5b and the duration of ADT. Based on the results of the study, BAP and TRACP-5b were weakly related to the duration of ADT ($r = 0.180$, $p = 0.0062$ and $r = 0.211$, $p = 0.0086$, respectively). We also found that BAP was significantly higher in patients with previous bone fractures of the spine or hip, and both BAP and TRACP-5b were significantly higher in patients with

Table 1 Patient characteristics

	Mean ± SD	Median (IQR)
Patients (*N*)	230	
Age (years)	76.6 ± 6.4	77.5 (74, 81)
Stage (UICC)		
I + II/III	171/59	
Content of ADT		
CAB/GnRH/preADT	63/88/79	
Reason for ADT ($N = 151$)[a]		
Primary ADT/BCF after RP/ADT with RT	116/29/6	
PSA when starting ADT (ng/dl)	21.6 ± 34.6	9.7 (4.9, 21.4)
Previous bone fractures of the spine or hip		
Present/absent	11/219	
Fracture during ADT		
Present/absent	9/230	
Family history of bone fracture of the spine or hip		
Present/absent	15/215	
Current smoking		
Present/absent	32/198	
Alcohol excess[b]		
Present/absent	9/221	
Hypertension		
Present/absent	123/107	
Diabetes		
Present/absent	40/190	
CKD 3		
Present/absent	80/150	
Rheumatoid arthritis		
Present/absent	2/228	
Steroid administration		
Present/absent	0/230	
BMI (kg/m^2)	23.2 ± 2.8	23.0 (21.3, 24.8)
BMI (categorical)		
Underweight/normal/overweight/obese	9/167/49/5	
Spinal fracture on radiography		
Present/absent	20/210	
Duration of ADT (months) ($N = 151$)[a]	37.4 ± 30.7	31 (13.5, 52.5)
Duration of ADT (biennial category)		
PreADT/<2 years/<4 years/<6 years/>6 years	79/63/47/21/20	

ADT androgen deprivation therapy, *CAB* combined androgen blockade, *GnRHa* gonadotropin-releasing hormone agonist, *BCF* biochemical failure, *RP* radical prostatectomy, *RT* radiation therapy, *PSA* prostate-specific antigen, *CKD* chronic kidney disease

[a]Pre-ADT patients are excluded

[b]Drinking >3 U of alcohol per day

spinal fracture on radiography than in patients without any fractures (Table 4).

A multivariate forward stepwise regression analysis was calculated to predict lumbar spine BMD based on diabetes, BMI, spinal fracture on radiography, the duration of ADT, and BAP. A significant regression equation [F (5, 224) = 12.925, $p < 0.0001$, with an R^2 of 0.224] found that the duration of ADT, BMI, diabetes, BAP, and spinal fracture on radiography were all significant predictors of lumbar spine BMD. Furthermore, a multivariate forward stepwise regression analysis was calculated to predict femoral neck BMD based on diabetes, BMI, age, spinal fracture on radiography, the duration of ADT, and BAP. A significant regression equation [F (4, 225) = 23.406, $p < 0.0001$, with an R^2 of 0.294] found that

Table 2 Comparison of BMD and bone metabolism markers according to ADT duration

ADT duration (years)	Pre	<2 years	<4 years	<6 years	>6 years	*p* value
N = 230	79	63	47	21	20	
Lumbar spine BMD (g/cm^2)	1.031 ± 0.218	0.994 ± 0.161	0.916 ± 0.218	0.935 ± 0.211	0.839 ± 0.186	0.0005
Lumbar spine *T*-score	− 0.086 ± 1.532	− 0.359 ± 1.127	− 0.909 ± 1.529	− 0.781 ± 1.482	− 1.435 ± 1.312	0.0005
Lumbar spine YAM	98.8 ± 20.9	95.2 ± 15.5	87.8 ± 20.9	89.6 ± 20.4	80.5 ± 17.9	0.0005
Femoral neck BMD (g/m^2)	0.692 ± 0.123	0.677 ± 0.106	0.624 ± 0.127	0.619 ± 0.117	0.603 ± 0.127	0.0014
Femoral neck *T*-score	−1.349 ± 0.973	−1.468 ± 0.827	−1.881 ± 1.001	−1.929 ± 0.933	−2.045 ± 1.003	0.0016
Femoral neck YAM	80.2 ± 14.3	78.4 ± 12.2	72.3 ± 14.7	71.8 ± 13.7	70.0 ± 14.8	0.0016
BAP (μg/l)	15.2 ± 6.3	16.5 ± 5.8	20.7 ± 9.0	16.8 ± 5.0	19.2 ± 6.0	0.0003
N = 81	3	30	26	12	10	
Urine NTx (nM BCE/mM·Cre)	31.7 ± 7.8	47.0 ± 16.4	57.7 ± 28.1	38.4 ± 14.7	57.2 ± 12.1	0.0239
N = 154	76	36	23	9	10	
TRACP-5b (mU/dl)	427.3 ± 207.4	553.0 ± 151.7	541.5 ± 151.2	409.0±139.0	589.2 ± 92.8	0.0007

YAM young adult mean, *BMD* bone mineral density, *BAP* bone alkarine phosphatase, *Urine NTx* urine N-terminal telopeptide, *TRACP-5b* tartrate-resistant acid phosphatase-5b

the duration of ADT, BMI, BAP, and spinal fracture on radiography were significant predictors of femoral neck BMD (Table 5). As a precaution, urine NTx and TRACP-5b were excluded from the multivariate analysis because each was only measured as a bone resorption marker in the patients. In summary, stepwise regression analyses revealed that the duration of ADT was a significant variable of both lumbar spine BMD and femoral neck BMD.

According to lumbar spine and femoral neck BMD, the number of patients who were normal, who had osteopenia, and who had osteoporosis were 58, 120, and 52, respectively, based on WHO criteria for the diagnosis of osteoporosis [9]. The prevalence of osteoporosis was 12.7% in hormone-naive patients, 11.1% in patients with <2 years of ADT, 44.7% in patients with 2–4 years of ADT, 23.8% in patients with 4–6 years of ADT, and 45.0% in patients with ≥6 years of ADT. Univariate analyses showed that as the duration of ADT increased, the prevalence of osteoporosis increased statistically ($p = 0.0002$) (Fig. 1). As with the duration of ADT, other variables—BMI, age, spinal fracture on radiography, and BAP—were also significant for the prevalence of osteoporosis in univariate analyses ($p < 0.0001$, $p < 0.0001$, $p = 0.0001$, and $p = 0.0002$, respectively). When diabetes, BMI, age, spinal fracture on radiography, duration of ADT, and BAP were included as predictor variables in multivariate logistic regression analysis to predict diagnosis of osteoporosis, the duration of ADT persisted as a significant variable after controlling simultaneously for potential confounders [OR 1.020 (1.008–1.032), $p = 0.0012$] (Table 6).

Discussion

Decreased BMD in prostate cancer patients receiving ADT is well documented in Western countries [2–5, 10, 11]. The present study showed that BMD decreased both at the lumbar spine and femoral neck as the duration of ADT increased. This result is compatible with those of previous studies. Loss of BMD means an increase in fractures in NMPC patients receiving ADT. In the present study, spinal fractures on X-rays were seen in 9.1% of subjects. On the other hand, the prevalence of vertebral fractures was 13–33% in the Caucasian population [12, 13]. White race and low BMD were significantly associated with vertebral fracture. Therefore, the differences in the prevalence of vertebral fracture between our study and other studies might be explained by ethnic differences [12].

To date, only a few studies discuss BMD loss associated with ADT for prostate cancer patients in the Asian population. Almost all of the studies were reported from Japan, but were either small in number or contained both non-metastatic and bone metastatic prostate cancer patients [14–17]. Yuasa et al. [14] showed that a decrease in BMD was associated with ADT in Japanese patients. In their study, lumbar spine, total hip, and femoral neck BMD was measured by DEXA, and the prevalence of osteoporosis was compared between 70 ADT-treated patients without bone metastasis and 88 hormone-naive patients. The results showed that although ADT-treated patients without

Table 3 Comparison of lumbar spine and femoral neck BMD according to patient characteristics

Factors	*N*	Lumbar spine BMD (g/m^2)[b]	*p* value	Femoral neck BMD (g/m^2)[b]	*p* value
Age (years)	230	− 0.083 (− 0.210 to 0.047)	NS	− 0.243 (− 0.361 to − 0.118)	0.0002
Stage (UICC)					
I + II	171	0.969 ± 0.206	NS	0.655 ± 0.117	NS
III	59	0.979 ± 0.208		0.674 ± 0.139	
Content of ADT					
CAB	63	0.919 ± 0.182	NS	0.637 ± 0.135	NS
GnRHa	88	0.956 ± 0.205		0.647 ± 0.108	
PSA when starting ADT (ng/dl)	230	0.042 (− 0.088 to 0.171)	NS	0.098 (− 0.031 to 0.225)	NS
Previous bone fractures of the spine or hip					
Present	11	0.905 ± 0.194	NS	0.625 ± 0.156	NS
Absent	219	0.975 ± 0.208		0.661 ± 0.121	
Fracture during ADT					
Present	9	0.905 ± 0.297	NS	0.630 ± 0.185	NS
Absent	221	0.943 ± 0.189		0.644 ± 0.115	
Family history of bone fracture of the spine or hip					
Present	15	0.979 ± 0.210	NS	0.669 ± 0.124	NS
Absent	215	0.971 ± 0.208		0.659 ± 0.115	
Current smoking					
Present	32	1.008 ± 0.193	NS	0.671 ± 0.119	NS
Absent	198	0.966 ± 0.210		0.658 ± 0.124	
Alcohol excess[a]					
Present	9	1.030 ± 0.206	NS	0.689 ± 0.147	NS
Absent	221	0.970 ± 0.208		0.659 ± 0.122	
Hypertension					
Present	123	0.993 ± 0.201	NS	0.661 ± 0.123	NS
Absent	107	0.948 ± 0.214		0.658 ± 0.124	
Diabetes					
Present	40	1.084 ± 0.214	0.0001	0.709 ± 0.134	0.0054
Absent	190	0.948 ± 0.199		0.649 ± 0.118	
CKD 3					
Present	80	0.986 ± 0.217	NS	0.654 ± 0.133	NS
Absent	150	0.964 ± 0.203		0.663 ± 0.117	
Rheumatoid arthritis					
Present	2	0.845 ± 0.041	NS	0.546 ± 0.006	NS
Absent	228	0.973 ± 0.208		0.661 ± 0.123	
BMI (kg/m^2)	230	0.267 (0.143 to 0.383)	< 0.0001	0.384 (0.268 to 0.489)	< 0.0001
Spinal fracture on radiography					
Present	20	0.841 ± 0.168	0.0029	0.549 ± 0.097	< 0.0001
Absent	210	0.984 ± 0.207		0.670 ± 0.120	
Duration of ADT (months)	230	− 0.243 (− 0.361 to − 0.118)	0.0002	− 0.212 (− 0.332 to − 0.085)	0.0012
BAP	230	− 0.251 (− 0.368 to − 0.126)	0.0001	− 0.317 (− 0.428 to − 0.195)	< 0.0001
Urine NTx	81	− 0.328 (− 0.509 to − 0.118)	0.0027	− 0.355 (− 0.532 to − 0.148)	0.001
TRACP-5b	154	− 0.162 (− 0.312 to − 0.004)	0.045	− 0.222 (− 0.367 to − 0.066)	0.0056

ADT androgen deprivation therapy, *CAB* combined androgen blockade, *GnRHa* gonadotropin-releasing hormone agonist, *PSA* prostate-specific antigen, *CKD* chronic kidney disease, *BAP* bone alkarine phosphatase (μg/l), *NTx* N-terminal telopeptide (nM BCE/mM·Cre), *TRACP-5b* tartrate-resistant acid phosphatase-5b (mU/dl)

[a]Drinking >3 U of alcohol per day

[b]Results of Pearson's correlation coefficient are described as *r* (95% CI)

Table 4 Association between factors of fracture and bone metabolism markers

Factors		*N*	BAP	*p* value	*N*	Urine NTx	*p* value	*N*	TRACP-5b	*p* value
Previous bone fractures of the spine or hip	Present	11	22.6	0.0078	4	66.0	NS	7	584.9	NS
	Absent	219	16.9		77	49.0		147	478.3	
Fracture during ADT	Present	9	19.0	NS	4	57.0	NS	5	519.6	NS
	Absent	221	17.1		77	49.5		149	481.9	
Spinal fracture on radiography	Present	20	20.6	0.0235	9	60.4	NS	11	594.5	0.0413
	Absent	210	16.9		72	48.5		143	474.6	

BAP bone alkarine phosphatase (μg/l), *NTx* N-terminal telopeptide (nM BCE/mM·Cre), *TRACP-5b* tartrate-resistant acid phosphatase-5b (mU/dl)

Table 5 Stepwise regression analyses to predict lumbar spine BMD and femoral neck BMD

	Lumbar spine BMD		Femoral neck BMD	
	SE *B*	*β*	SE *B*	*β*
Diabetes	0.033	0.202	–	–
BMI (kg/m^2)	0.004	0.225	0.002	0.348
Spinal fracture on radiography	0.044	− 0.121	0.025	− 0.181
Duration of ADT (months)	0.0004082	− 0.215	0.0002295	− 0.166
BAP (μg/l)	0.002	− 0.151	0.001	− 0.236

R^2 value 0.224, adjusted R^2 0.207, $p < 0.0001$ for lumbar spine BMD; R^2 value 0.294, adjusted R^2 0.281, $p < 0.0001$ for femoral neck BMD

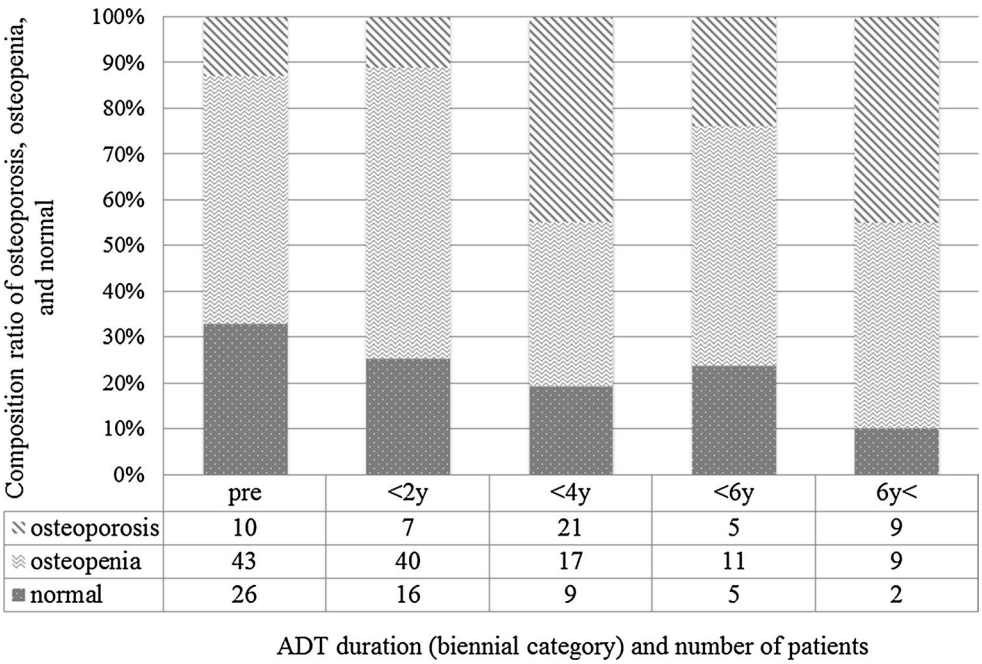

Fig. 1 Changes in the prevalence of osteoporosis stratified by ADT duration (biennial category); as the duration of ADT increased, the prevalence of osteoporosis increased ($p = 0.0002$), reaching 45% in patients with ≥6 years of ADT

bone metastasis had significantly lower BMD values than hormone-naive patients, their ADT treatment (on average 30.7 months) did not increase the prevalence of osteoporosis. These findings are different from the results of our study which show the prevalence of osteoporosis and osteopenia were 12.7 and 36.7% in hormone-naive patients and 39.8 and 42.0% in patients receiving >2 years of ADT, respectively, and the prevalence of osteoporosis was positively associated with the duration of ADT in multivariate analysis. On the other hand, other studies from Western countries showed that prostate cancer patients undergoing ADT had a high incidence of osteoporosis. For example,

Table 6 Logistic regression analyses to predict diagnosis of osteoporosis

	OR (95% CI)	*p* value
Age (years)	1.089 (1.009–1.175)	0.0284
Diabetes	0.258 (0.065–1.020)	0.0533
BMI (kg/m^2)	0.704 (0.594–0.835)	< 0.0001
Spinal fracture on X-ray	5.275 (1.692–16.448)	0.0042
Duration of ADT (months)	1.020 (1.008–1.032)	0.0012
BAP (μg/l)	1.067 (1.014–1.123)	0.0121

OR 1.020 (1.008–1.032), $p = 0.0012$

Morote et al. [2] reported that 35.4 and 45.2% of hormone-naive patients had osteoporosis and osteopenia, respectively, while 42.9 and 39.3% of patients treated with ADT for 2 years suffered from osteoporosis and osteopenia, respectively. The finding that Japanese patients had a lower baseline incidence of BMD loss and osteoporosis was confirmed in our study as well as in the study by Yuasa et al. However, our study's finding, i.e., that as the duration of ADT increased the prevalence of osteoporosis increased, was compatible with the findings for Caucasians. As Yuasa et al. mentioned, there may be some racial differences that determine the BMD between Japanese and Caucasians. However, it seems reasonable that as BMD decreases with ADT, the prevalence of osteoporosis increases. We speculated that the reasons why there was no difference in the prevalence of osteoporosis between hormone-naive patients and ADT-treated patients in the study by Yuasa et al. were because the number of ADT-treated patients was small, the duration of ADT was relatively short, it included 6 patients treated with bicalutamide monotherapy and 3 patients using estramustine phosphate, and the baseline incidence of BMD loss in Japanese patients was low. To confirm the differences among these studies in Japanese patients, larger scale and prospective studies are warranted.

While numerous risk factors have been identified for postmenopausal osteoporosis, including age, personal or family history of fracture, Asian or Hispanic heritage, smoking and cortisone use, only a few studies have examined lifestyle factors in androgen-deprived patients with prostate cancer [18]. In the present study, some lifestyle factors associated with osteoporosis were investigated in NMPC patients with ADT, and BMI was confirmed as the strongest predictor for BMD and osteoporosis among several variables, including the duration of ADT. To date, studies examining the relationship between body composition and bone mass have found conflicting results. Although a few studies found that individuals with higher BMI levels have a higher risk of osteoporosis, the majority of studies using BMI as an indicator of adiposity have primarily found obesity to be protective against osteoporosis [19]. On the other hand, the inverse relationship between underweight and BMD is well understood, although in postmenopausal women it was clearly shown that low BMI was an important risk factor for low bone mass and increased bone loss [20]. Ryan et al. [21] showed that BMI was positively associated with Z-scores at the femoral neck and total hip after adjusting for the duration of ADT and other lifestyle factors in androgen-deprived patients with prostate cancer. However, the duration of ADT, not BMI, was the strongest predictor for BMD. The differences in the power of predicting osteoporosis between the duration of ADT and BMI in the study by Ryan et al. and the present study may be due to the difference in the distribution of BMI. In the study by Ryan et al., most patients were overweight or obese, with a median BMI of 28.8 kg/m^2; however, in our study, most patients were in the normal range, with a median BMI of 23.0 kg/m^2. Elderly Japanese men, who usually have a lower BMI than elderly Caucasians, may be more susceptible to the influence of BMI on BMD. It should be mentioned that BMI as well as ADT is one of the most important factors affecting bone mass and osteoporosis in Japanese prostate cancer patients with ADT. On the other hand, some lifestyle diseases are related to BMD and osteoporosis. In particular, diabetes and CKD are well known as being related to fracture risk. The present study showed that diabetes was positively associated with BMD in multivariate analyses. This finding is compatible with the results of a meta-analysis that found BMD increased in patients with type 2 diabetes [22]. To our knowledge, this is the first study to reveal a relationship between BMD and diabetes in prostate cancer patients undergoing ADT.

A limitation of the study is that it was cross-sectional and retrospective, and the number of patients was relatively small. Additionally, patients grouped according to the duration of ADT might not be comparable at the time of starting ADT. There should be some differences within each group, and long-term ADT might affect their backgrounds. To eliminate this concern, prospective longitudinal studies will be necessary. Serum testosterone was not investigated in this study, so we did not confirm whether patients receiving ADT were castrated. Since we did not measure serum testosterone levels in patients in this study, we could not confirm whether patients undergoing ADT were in castration. However, we were strictly administering GnRHa on schedule, so we considered that almost all patients undergoing ADT were castrated [23]. Moreover, we did not investigate some other factors that could possibly affect BMD, such as sex hormones (including testosterone and estrogen), factors related to calcium metabolism (including parathyroid hormone, thyroid-stimulating hormone, calcium, and vitamin D), and lifestyle factors (including calcium and vitamin D intake and amount of exercise) [24]. Additionally, this study was carried out on the basis of daily practice, so only urine NTx

or TRACP-5b was measured as a bone resorption marker in each patient because of the medical insurance restriction. For this reason, bone resorption markers were not added to the multivariate analyses.

Conclusion

This study showed that ADT negatively affected lumbar spine and femoral neck BMD in Japanese patients with NMPC. As the duration of ADT increased, BMD decreased at both sites. We also observed a progressive increase in the prevalence of osteoporosis in Japanese NMPC patients with ADT. The prevalence of osteoporosis reached 45% after 6 years of ADT. In addition, we investigated patient backgrounds in detail for anything that may possibly affect BMD in the Asian population, and we showed for the first time a positive relationship between BMD and diabetes in prostate cancer patients undergoing ADT. Larger scale and prospective studies are warranted to clarify ethnic differences in the prevalence of osteoporosis accompanying ADT in prostate cancer patients of Asians and Caucasians.

Acknowledgements We thank the patients of Ogaki Municipal Hospital (Ogaki, Japan).

Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this type of study formal consent is not required.

Informed consent Informed consent was obtained from all individual participants included in the study.

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