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Comparison of bone mineral loss by combined androgen block agonist versus GnRH in patients with prostate cancer: A 12 month-prospective observational study

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The multi-centre, prospective, observational study was designed to examine the efficacy of continuous combined androgen block (CAB) vs. GnRH agonist monotherapy in terms of bone mineral density (BMD) change during 12 months post-androgen deprivation therapy (ADT) in Asian prostate cancer patients. Multiple regression analysis and estimated the 10-year probability of major fractures among the patients with Fracture Risk Assessment Tool were conducted to investigate the underlying factors affecting BMD. Paired t-test to evaluate the change of BMD from baseline to 12 month, and two sample t-test to examine the difference of BMD changes were used between two groups. BMD significantly decreased in both the CAB and GnRH groups, with no group wise differences. The proportion of osteopenia or osteoporosis was slightly increased after the 12-month post-ADT. Ten-year probability of hip fracture and major osteoporotic fracture was approximately 3% and 5%, respectively. In conclusion, a significant decrease of BMD by 12-month ADT was observed without any differences between the two groups, whereas ADT-related BMD loss did not induce detrimental effects on bone health in terms of increased bone fracture risk. This was the first prospective study on BMD changes as a predictor of fracture during ADT in an Asian population.

The worldwide increase in lifespan and improving medical technologies in diagnostic and therapeutic areas such as PSA screening facilitate earlier prostate cancer detection resulting in the most rapid increase in cancer among men¹. Asian countries also showed rapid increase of prostate cancer incidence similar to Western countries, but with relatively lower incidence. The annual increase rate of prostate cancer in Korea clearly indicates that prostate cancer is the second most rapidly increasing Asian male cancer with an annual increase of 12.3% among all cancers^{2,3}. Increasing number of early diagnosed prostate cancer cases have better prognoses, however, a significant portion of newly diagnosed patients still have advanced prostate cancer including metastatic disease and androgen deprivation therapy (ADT) is a standard treatment for such patients⁴.

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The ADT comprises two different therapeutic regimens⁴. One regimen comprises either orchiectomy or gonadotropin-releasing hormone (GnRH) agonist that reduces testosterone and oestrogen concentrations; and the other of nonsteroidal androgen receptor blocker called bicalutamide that maintains testosterone and oestrogen concentrations. The bicalutamide ADT is reportedly less effective than ADT either with orchiectomy or GnRH agonist in metastatic diseases. Another combination regimen of strengthening the efficacy was the combined androgen block (CAB) with GnRH agonist plus bicalutamide, which has significant advantages over castration alone or GnRH agonist monotherapy, such as a higher proportion of patients with complete and partial responses, improved control of pain associated with metastatic disease, longer disease-free survival, and longer overall survival by an average of 3–6 months, as compared with combined treatment with the anti-androgen initiated later^{4–6}.

However, one of the adverse effects of ADT is poor bone health due to significant decreases in bone mineral density (BMD) by 1.5–4.0% annually⁷. Combined with the underlying low BMD presented as osteopenia or osteoporosis in mostly old-aged patients with prostate cancer⁸, ADT-induced bone mineral loss that presents as osteopenia or osteoporosis is a major adverse outcome with the increasing risks of serious complications such as lumbar and hip fractures^{9–11}. Based on the nationwide analysis of Swedish Prostate Cancer Registry, men on ADT represented an additional 30 deaths per 1000 person-years in men who develop hip fractures, as compared with an additional 20 deaths per 1000 person-years for hip fractures in the general male population^{10,11}.

Prior experimental work showed that bone turnover markers including urinary N-telopeptide and serum osteocalcin are elevated in men receiving GnRH agonist but not in men receiving bicalutamide monotherapy, which suggests that bicalutamide monotherapy may maintain BMD and potentially prevent fracture¹². However, comparative evaluation of BMD loss between treatment groups such as CAB and GnRH agonist monotherapy has not been previously conducted. Therefore, the study was aimed to examine the effect of CAB vs. GnRH agonist monotherapy on BMD change and to determine the underlying factors affecting BMD during 12 months post-treatment initiation in prostate cancer patients and the 10-year probability of major fractures.

Patients and Methods

Ethical statements. All study protocols were conducted according to the ethical guidelines of the 'World Medical Association Declaration of Helsinki-Ethical Principles for Medical Research Involving Human Subjects'. This study was approved by the ethics committees and the Institutional Review Boards at each hospital (10 University hospitals in South Korea which were National Cancer Center, Severance Hospital, Konkuk University Medical Center, Seoul, Seoul National University Hospital, Seoul St. Mary's Hospital, Samsung Medical Center, Seoul National University Bundang Hospital, Seoul National University Boramae Medical Center, Korea Cancer Centre Hospital, and Asan Medical center), that participated in the study, including the Institutional Review Board of the Research Institute and Hospital of Asan Medical Center (IRB No. 2010-0210), and all enrolled patients provided written informed consent.

Study design. The study was originally designed as a non-inferiority, multi-centre (10 University hospitals in metropolitan of Seoul, South Korea which were National Cancer Center, Severance Hospital, Konkuk University Medical Center, Seoul, Seoul National University Hospital, Seoul St. Mary's Hospital, Samsung Medical Center, Seoul National University Bundang Hospital, Seoul National University Boramae Medical Center, Korea Cancer Centre Hospital, and Asan Medical center), prospective trial on patients who were eligible for study enrolment between April 2011 and February 2014. By the statistical calculation performed by medical statistician (SK, PhD), 416 patients were needed for a one-sided type I error of 2.5% and a power of 90% with –1.5% of non-inferiority margin for change of BMD of L-spine. Assuming a 20% follow-up loss, we needed 500 patients (250 per treatment group). However, because of non-intervention and non-randomization nature, the enrolment was imbalanced between GnRH group (n = 70) and CAB group (n = 242). Data safety monitoring board (DSMB) reviewed the enrolment status and decided to stop the study earlier than planned. Hence, the limited results of this study were finally designed as a prospective, non-interventional observation cohort study. The study was also conducted in a routine clinical practice without affecting patient treatment. There is no definite standard treatment in terms of ADT options including CAB and monotherapy.

Patients' enrolment criteria. A total of 312 target subjects were pathologically diagnosed prostate cancer patients aged ≥ 50 , and patients who were scheduled to receive either continuous ADT with CAB (CAB group, n = 70) or GnRH agonist monotherapy (GnRH group, N = 242) by each physician's discretion after considering the following criteria: BMD was measured in all patients before ADT initiation. Patients who had a lowered T-score ≤ -3.0 at the time of enrolment and withdrawn their consent were excluded. Patients did not receive denosumab or bisphosphonates such as pamidronate or zoledronic acid during ADT. After the 8 subjects with exclusion criteria and 51 patients with early drop-out during the study, a final of 253 patients including 196 patients in the CAB group and 57 patients in the GnRH group completed the study (Table 1).

Bone mineral densitometry. BMD was measured by Dual energy x-ray absorptiometry (DEXA) in 10 site hospitals. The BMD of L-spine from L1-4 and total, and BMD of femur total and femur neck were measured. Using BMD values, T-score and Z-score were calculated by conventional method. The BMD values at baseline and at 12M (12th month from treatment initiation) were collected at the study site.

Fracture risk assessment. Estimation of the 10-year probability of major fractures was by the Fracture Risk Assessment Tool (FRAX[®]) with BMD. The factors included age, sex, body mass index, alcohol use, tobacco use, glucocorticoid use, rheumatoid arthritis, previous fragility fracture, family history of hip fracture, and secondary osteoporosis, and T-score of femur neck BMD.

Parameter		CAB group N = 234		GnRH group N = 70		p-value
Age (mean \pm SD, Yr)			70.70 \pm 7.83		72.24 \pm 8.63	0.1593 [§]
(N,%)	50~59	22	9.40	5	7.14	0.1178 [‡]
	60~69	69	29.49	20	28.57	
	70~79	119	50.85	30	42.86	
	≥ 80	24	10.26	15	21.43	
BMI (mean \pm SD, kg/m ²)		23.90	± 2.91	23.77	± 2.91	0.7507 [§]
Past or present smoking history (N,%)	Present smoker	24	10.26	9	12.86	0.2898 [†]
	Ex-smoker	88	37.61	32	45.71	
	Never smoker	122	52.14	29	41.43	
Present smoker (N,%)		24	26.69 \pm 17.23	9	29.78 \pm 14.59	0.6371 [§]
Present non-smoker (N,%)		88	25.32 \pm 21.67	32	35.41 \pm 29.25	0.0714 [‡]
Alcohol consumption (N,%)		128	54.70	44	62.86	0.2271 [†]
Amount of alcohol consumption (N,%)	≥ 2 units/day*	52	40.63	10	22.73	0.0329 [†]
	< 2 units/day*	76	59.38	34	77.27	
Fracture history (N,%)		19	8.12	5	7.14	0.7903 [†]
Family history of hip fracture (N,%)		1	0.43	0	0.00	1.0000 [‡]
Concomitant medication (N,%)		96	41.03	38	54.29	0.0499 [†]
Osteoporosis-related concurrent disease (N,%)		3	1.28	1	1.43	1.0000 [‡]
initial PSA (mean \pm SD, ng/mL)			213.46 \pm 1287.05		30.60 \pm 60.15	0.1573 [‡]
Gleason score (mean \pm SD)			7.76 \pm 1.06		7.77 \pm 1.20	0.9671 [§]
Prostate volume (mean \pm SD, cc)			52.09 \pm 29.16		38.84 \pm 16.05	0.0017 [‡]
Clinical stage at diagnosis	Tx	3	1.28	0	0.00	0.0616 [‡]
	T0	1	0.43	0	0.00	
	T1	30	12.82	5	7.25	
	T2	65	27.78	29	42.03	
	T3	103	44.02	32	46.38	
	T4	32	13.68	3	4.35	
	N0	164	70.09	61	88.41	0.0022 [†]
	N1	70	29.91	8	11.59	
	M0	180	76.92	60	86.96	0.0711 [†]
	M1	54	23.08	9	13.04	
Treatment for prostate cancer	Surgery	92	41.63	34	50.75	
	RRP	46	50.00	25	73.53	
	LRP	2	2.17	0	0.00	
	RALP	36	39.13	7	20.59	
	Other	8	8.70	2	5.88	
	Radiation	21	9.50	2	2.99	
	Primary	18	85.71	1	50.00	
	Palliative	3	14.29	1	50.00	
	None	116	52.49	32	47.76	

Table 1. Demographic characteristics. [§]Two sample *t*-test; [‡]Wilcoxon's rank sum test; [†]Pearson's chi-square test; [‡]Fisher's exact test; [‡]Overlapped count; *Alcohol 2 units \equiv beer 1 bottle (500 mL), Korean whisky (Soju) 1/4 bottle (90 mL), Korean rice wine 1 bottle (500 mL), Wine 2 glasses (200 mL) or Whisky 2 glasses (60 mL)) RRP: radical retropubic prostatectomy; LRP: laparoscopic radical prostatectomy; RALP: robotic-assisted laparoscopic prostatectomy.

Statistical analysis. We evaluated the primary objective as the changes in BMD from baseline to 12-month from ADT initiation. The changes from baseline to 12-month were evaluated by paired *t*-test, and the difference between the treatment groups was evaluated by 2 sample *t*-test. Using the lowest T-score among L-spine total, femur total or femur neck at baseline and 12M, BMD status was graded as normal (T-score ≥ -1.0), osteopenia ($-2.5 < \text{T-score} < -1.0$), and osteoporosis (T-score ≤ -2.5)¹¹. In addition, the number and proportion of subjects with osteopenia or osteoporosis were analysed with Pearson's chi-square test. We also evaluated the underlying factors affecting BMD changes from baseline to 12M, by multiple regression analysis with treatment group, age, weight, and history of smoking and alcohol drinking as independent variables. FRAX[®] scores of baseline, 12M and the change from baseline to 12M by treatment groups were evaluated by paired *t*-test. The difference between the treatment groups was evaluated by 2 sample *t*-test. Additionally, we evaluated the incidence of skeletal-related events (SREs) at baseline, 12M and the change from baseline to 12M by treatment group by Fisher's exact test. We adjusted the potential effect of exercise on BMD change by using the International Physical Activity Questionnaire (IPAQ).

Time	Diagnosis	CAB group (N = 234)		GnRH group (N = 70)		p-value
		n	(%)	n	(%)	
Baseline	n	234		70		
	Normal ($T \geq -1.0$)	120	(51.28)	35	(50.00)	0.9427 [†]
	Osteopenia ($-2.5 < T < -1.0$)	92	(39.32)	29	(41.43)	
	Osteoporosis ($T \leq -2.5$)	22	(9.40)	6	(8.57)	
12 month	n	186		55		
	Normal ($T \geq -1.0$)	81	(43.55)	20	(36.36)	0.3688 [†]
	Osteopenia ($-2.5 < T < -1.0$)	81	(43.55)	24	(43.64)	
	Osteoporosis ($T \leq -2.5$)	24	(12.90)	11	(20.00)	

Table 2. Proportion of osteopenia or osteoporosis. [†]Pearson's chi-square test.

Results

Baseline characteristics. Among the 253 patients who completed the study, no differences in demographic characteristics between treatment CAB (n = 196) and GnRH (n = 57) groups were observed including occurrence of osteoporosis-related concurrent disease ($p > 0.05$, Table 1 and Supplementary Table 1); except for their prostate volume (52.09cc in CAB group vs. 38.84cc in GnRH group), clinical N stage (N1, 29.91% vs. 11.59%), mean daily alcohol consumption of approximately ≥ 2 units (40.63% vs. 22.73%) and administration of concomitant medications (41.03% vs. 52.29%) ($p < 0.05$, Table 1 and Supplementary Tables 1 and 2).

As for the rate of osteoporosis and osteopenia, 39.32% (92/234 subjects) of the CAB group had osteopenia and 9.40% (22/234 subjects) had osteoporosis at baseline, whereas 41.43% (29/70 subjects) of the GnRH group had osteopenia and 8.57% (6/70 subjects) had osteoporosis at baseline.

Changes in BMD. At 12M, the proportion of the subjects with osteopenia or osteoporosis was slightly increased, but the difference between the groups was not significant ($p = 0.3688$; Table 2). As shown in Table 3, there were statistically significant mean decrease changes from baseline to 12-month in L-spine total BMD in both groups with -0.04 (SD 0.14) in the CAB group ($p < 0.00090$) and -0.05 (SD 0.19) in the GnRH group ($p < 0.001$). The rate of BMD change in L-spine also significantly decreased 2.61% in the CAB group ($p < 0.009$) and 4.37% in the GnRH group ($p < 0.0001$) with a 95% confidence interval of $[-2.04\%, 5.57\%]$. Non-inferiority of the CAB group was undetermined with the lower limit of 95% confident interval of $< -1.5\%$, however, the group wise difference was not statistically significant ($p = 0.1518$). Furthermore, BMD significantly decreased in L1-L4 of both groups, but there were no differences between the 2 groups ($p > 0.05$; Supplemental Table 3).

The results showed a statistically significant decrease in L-spine total T-score in both groups with 0.34 in the CAB group and 0.43 in the GnRH group, respectively ($p < 0.0001$; Supplemental Table 4). However, the difference between the groups was not statistically significant ($p = 0.4228$).

The changes of each T-score of L1-L4 had the same pattern as total T-score. The L-spine total Z-score decreased in both groups with 0.30 in the CAB group ($p < 0.0001$) and 0.34 in the GnRH group ($p = 0.0006$), without significant differences between treatment groups ($p = 0.8123$; Supplemental Table 5). Likewise, the BMD of total femur and femur neck, T-score and Z-score were significantly decreased from baseline to 12M in both groups, with no significant differences between the groups (Supplemental Tables 6, 7 and 8).

Estimated 10-year probability of major fractures. According to FRAX[®], the mean 10-year probability of major osteoporotic fracture at 12-month was 4.96% and 5.85% in the CAB and GnRH groups, respectively, which was not significantly changed from baseline in both groups, with no significant group wise differences ($p > 0.05$, Table 3).

The 10-year probability of hip fracture at 12M was 1.69% and 2.41% in the CAB and GnRH groups, respectively. Significant increase from baseline by $0.20 \pm 1.16\%$ ($p = 0.0231$) was observed in the CAB group, while there was no statistically significant change over basal values in the GnRH group, and no differences between the groups ($p = 0.5531$). Two subjects in the GnRH group presented with pathologic fracture and received bone surgery with adjuvant radiation therapy at the time of participation. No new SRE occurred in both groups during ADT (Supplemental Table 9).

Factors affecting the change in BMD. Factor analysis showed that the treatment group was not a significant risk factor for BMD change ($p > 0.05$, Table 4). For L-spine BMD, there were no factors affecting either T-score or Z-score among treatment groups, age, body weight, smoking and alcohol consumption ($p > 0.05$).

Despite the only significant effect of age on the change in L-spine BMD score ($p = 0.0285$, Table 4), the clinical effect was insignificant based on the regression estimate. For total femur, similar to L-spine, age was also a significant factor affecting the change in BMD (BMD score: $p = 0.0445$, T-score: $p = 0.0372$, Z-score: $p = 0.0267$), however, the clinical effect was insignificant (BMD score: $e = 0.001$, T-score: $e = 0.007$, Z-score: $e = 0.009$) (Supplemental Table 10). On the other hand, there were no factors affecting the change in BMD (BMD score, T-score, Z-score) for femur neck.

Exercise activity. At baseline, 67.52% (158/232 subjects) in the CAB group and 91.43% (64/70 subjects) in the GnRH group responded that they performed exercise, which was significantly different ($p < 0.0001$, Supplemental Table 11). At 12-month, 69.35% (138/199 subjects) and 80.70% (46/57 subjects) in the CAB and

Variable	Time	CAB group (N = 234)	GnRH group (N = 70)	Difference 95% C.I.	Between groups <i>p</i> -value ^a		
Total bone marrow density (BMD) score at L-spine							
Changes in total BMD score		n	Mean ± SD	n	Mean ± SD		
	Baseline	223	1.16 ± 0.25	63	1.15 ± 0.22		0.8636 [§]
	12 Month	184	1.13 ± 0.26	55	1.09 ± 0.19		
		176	−0.04 ± 0.14	48	−0.05 ± 0.06	0.01 (−0.03, 0.06)	0.4887 [§]
	Within group <i>p</i> -value	0.0009 ^{§§}		<0.0001 ^{§§}			
Rate of BMD change		176	−2.61 ± 13.11	48	−4.37 ± 5.04	1.77(−2.04, 5.57)	0.1518 [§]
	Within group <i>p</i> -value	0.0090 ^{§§}		<0.0001 ^{§§}			
FRAX [®] score of major osteoporotic and hip fractures							
Major osteoporotic fracture (%)	Baseline	234	5.08 ± 3.14	70	5.35 ± 2.75		0.5194 [§]
	12 month	186	4.96 ± 2.84	55	5.85 ± 3.48		
	change	186	−0.23 ± 2.79	55	0.20 ± 2.74		0.3189 [§]
	Within group <i>p</i> -value	0.2635 ^{§§}		0.5973 ^{§§}			
Hip fracture (%)	Baseline	234	1.50 ± 1.54	70	1.87 ± 1.78		0.0943 [§]
	12 month	186	1.69 ± 1.76	55	2.41 ± 2.53		
	change	186	0.20 ± 1.16	55	0.36 ± 1.97		0.5531 [§]
	Within group <i>p</i> -value	0.0231 ^{§§}		0.1798 ^{§§§}			

Table 3. Total bone mineral density (BMD) score at L-spine and FRAX[®] score for major osteoporotic and hip fractures. Change = score at 12 month – score at baseline Rate of BMD change = (BMD score at 12 month – BMD score at baseline)/BMD score at baseline \times 100 Difference = CAB group – GnRH group ^a*p*-value of difference between groups (CAB group – GnRH group): [§]Two sample *t*-test ^{§§}Paired *t*-test.

GnRH groups, respectively maintained exercise activity, which was not significantly different ($p = 0.0927$). In order of frequency, exercise of low-intensity was most common, followed by medium- and heavy-intensity.

Discussion

The indications for ADT in prostate cancer treatment have recently extended beyond standard use for palliation of metastatic prostate cancer¹³. Patients with ADT in adjuvant or combined therapy even in earlier stage cancers have increased, hence ADT-related side effects including bone health problems such as osteoporosis, lumbar or hip fractures by bone mineral loss are also of clinical relevance. This prospective observational study examined the effect of CAB vs. GnRH agonist monotherapy on longitudinal BMD change and calculated the 10-year probability of major fractures to determine the underlying factors affecting the ADT-related, but not tumour-related risk factors of BMD change during 12 months post-ADT initiation in prostate cancer patients.

The rapid increase of bone mineral loss and the continuous decrease of BMD within 1 year of ADT initiation are well described¹⁴. In the literature review of prospective studies, a wide range of BMD changes is influenced in patients who received ADT by different types of ADT, period of ADT, and patient ethnicity or presence of bone metastasis^{12–21}. In the present study, although the degree of BMD decrease was observed in both, the CAB group and GnRH group without any statistical differences between groups ($p = 0.8636$, Table 2), the total BMD score of L-spine showed significantly smaller change in the CAB group, as compared to the GnRH group ($p < 0.05$, Table 2). Many studies on bone mineral loss in patients with prostate cancer have shown that BMD decrease of L-spine ranges from 2.40% to 4.80% post-ADT for ≤ 12 months, which was similar to our results of 2.58% in the CAB group and 4.37% in the GnRH group^{14–23}.

In spite of the insignificant differences in clinical M stage and significant differences in clinical N stage (N1/M1, CAB 29.91%/23.08% vs. GnRH 11.59%/13.04%, $p = 0.0022/0.0711$) between CAB and GnRH groups, depending on the presence of bone metastasis, a 6.6% decrease in lumbar spine BMD and a 6.5% decrease in femoral neck BMD after 6 months of CAB were observed in patients with bone metastasis¹⁴ (Table 1). In patients without bone metastases, 2 studies showed that BMD decreases at 12M post-ADT with GnRH agonist were 3.9% and 4.8% of total BMD of L-spine, which represents a lower degree of BMD decrease than patients with bone metastasis^{19,22}, similar to the degree of BMD decrease in our previous results including cases without bone metastasis⁸, because the subjects with bone metastasis in our study constituted $<20\%$ of the entire study population.

Ethnic variation including genetic, hormonal or other environmental factors could potentially affect BMD change by ADT. African Americans older than 65 years have significantly higher BMD with a similar decline in BMD as compared to Caucasians^{24,25}, which may explain the reduced incidence of hip fracture in African Americans, as compared to Caucasians²⁵; whereas, another study on Jamaican men showed ADT with lower BMD²⁶. Some different cross-sectional Asian studies reported that Short-term ADT of an average 23.5 months did not increase the risk of osteoporosis in Japanese prostate cancer patients and ADT was not a significant risk factor for decreased BMD^{27,28}. Japanese men exposed to ADT have lower rates of osteoporosis with 2.3% and 8.6% in the hormone-naïve and ADT-treated patients, respectively, which was not statistically significant ($p = 0.294$).

variable	factor	Estimate	Standard Error	p-value
BMD (g/cm ²)	Group (1 = CAB group, 0 = GnRH group)	0.019	0.021	0.3699
	Age	0.002	0.001	0.0285
	Body weight	−0.001	0.001	0.3052
	Smoking history (1 = yes, 2 = no)	−0.009	0.021	0.6502
	Alcoholic history (1 = yes, 2 = no)	−0.021	0.021	0.3001
Total T-score	Group (1 = CAB group, 0 = GnRH group)	0.118	0.153	0.4432
	Age	0.014	0.008	0.0723
	Body weight	−0.004	0.007	0.5743
	Smoking history (1 = yes, 2 = no)	−0.024	0.152	0.8731
	Alcoholic history (1 = yes, 2 = no)	−0.115	0.149	0.4416
Total Z-score	Group (1 = CAB group, 0 = GnRH group)	0.046	0.156	0.7689
	Age	0.010	0.008	0.2091
	Body weight	−0.007	0.006	0.2669
	Smoking history (1 = yes, 2 = no)	−0.007	0.145	0.9617
	Alcoholic history (1 = yes, 2 = no)	−0.101	0.144	0.4851

Table 4. Factors affecting the change in L-spine BMD.

However, this study showed that the proportion of patients with osteopenia or osteoporosis was insignificantly increased slightly at 12M post-ADT initiation between groups ($p > 0.05$, Table 3) and osteoporosis was 9.4% of hormone-naïve Korean prostate cancer patients with an average age of 65.1, which is more common than the 3.4% of healthy controls in Korea ($p = 0.001$) and corresponding Japanese prostate cancer patients of an average age of 68.1⁸. As shown in literature reviews (Table 5), most prospective ADT studies were composed of patients from Western countries using GnRH agonists or orchiectomy, and only a few prospective studies from patients with CAB and only a few non-prospective, cross-sectional Asian studies have published their ADT-related results of bone mineral loss^{27–30}. This study has clinical relevance because it is the first prospectively designed study of longitudinal BMD changes by different types of ADT including CAB and GnRH agonists in Asian patients.

Bicalutamide monotherapy does not facilitate any bone mineral loss, which differs from BMD change due to GnRH agonist, orchiectomy or CAB¹². There is no prospective study, to the best of our knowledge that compares the rate of bone mineral loss depending on the types of ADT including GnRH agonist, orchiectomy or CAB. Instead, one retrospective cohort study including 742 patients presented a higher hazard ratio of fractures in patients treated with CAB than GnRH agonist, but this result may be confounded by pathologic and not ADT-related osteoporotic fractures³¹. A Jamaican cross-sectional study showed GnRH agonist, orchiectomy and CAB were a higher risk for osteoporosis than oestrogens or antiandrogen monotherapy. On adjusting for duration of therapy, the odd ratio (OR) of CAB was 9.2, as compared to oestrogens as a reference drug ($p < 0.003$), and the 4.5 OR of GnRH agonist ($p < 0.04$)²⁶. This differed from our finding of no additional risk of CAB, as compared with GnRH agonist monotherapy in terms of bone mineral loss. Although the authors adjusted age and duration of ADT treatment, they did not consider various life styles such exercise activity or dietary factors that could modify BMD loss due to the limited design of cross-sectional study vs. prospective study. However, in this study, we evaluated the characteristics of patient life styles, which further strengthened the study (Tables 1 and 4, Supplementary Tables 3 and 12).

Since 2005, large database analyses found an increased risk of developing fracture within 5 years in about 20% of men starting on ADT³². The prevalence of osteoporosis in men on ADT has substantial variation from 9 to 53% based on the results of a meta-analysis of 13 reports published from 1999 through 2012³³. An increased proportion of patients with osteopenia or osteoporosis were found at 12M from initiation of ADT, similar to this study, which showed slight increase at 12M post-ADT initiation between groups ($p > 0.05$, Table 2). However, the clinical relevance of those changes is necessarily important in terms of fracture risk related with ADT in prostate cancer. BMD measurement by DEXA is the standard test for bone health in men on ADT, but there are many concerns of its inaccurate prediction of fracture risk³⁴. The FRAX score in this study developed through risk prediction algorithms that estimate fracture probability using multiple risk factors for fracture, to compensate for this limitation of BMD measurement^{34,35}. The National Comprehensive Cancer Center Network and other published guidelines recommend screening men receiving ADT according to guidelines from the National Osteoporosis Foundation for the general population³⁴. They recommend drug therapy for men with a 10 year probability of hip fracture $>3\%$ or a 10 year probability of major osteoporosis-related fracture $>20\%$, as estimated using FRAX. In this study, the 10-year probability of hip fracture at 12M was $<3\%$, and the 10-year probability of major osteoporotic fracture was approximately 5% (Table 3). Accordingly, the BMD loss induced by ADT for 12 months did not induce detrimental effects on bone health in terms of increased risk of bone fracture in this study.

Some limitations persist despite the prospective design including multi-centres and its non-interventional nature. Firstly, a limited number of patients completed the study and an imbalance in number of subjects per group occurred, especially the small number of subjects enrolled in GnRH group. However, the study was basically designed as a non-interventional and non-randomized study with participants arbitrarily distributed in each treatment group. Although the non-inferiority of the CAB group was not determined with statistical significance through the study, we found a significant decrease in BMD and increased proportion of osteoporosis at 12M post-ADT. Secondly, we used the FRAX score to estimate the risk of fracture. However, version of Korean

Country	Stage	n	Type of ADT	Change in BMD	
Australia ¹⁴	M1	12	CAB	−6.6% at 6 mo	L spine
Sweden ¹⁵	M0	11	Orchiectomy	−10% at 12 mo	Proximal femur
France ¹⁶	M0	12	GnRH agonist	−4.6% at 12 mo −3.9% at 12 mo	L spine Femoral neck
USA ¹⁷	M0	10 16	Orchiectomy GnRH agonist or CAB	−2.4% at 12 mo −3.4% at 12 mo	Femoral neck
USA ¹⁸	M0	15	GnRH agonist	−2.8% at 12 mo	spine
Australia ¹⁹	M0	26	GnRH agonist	−3.9% at 12 mo	L spine
USA ²⁰	M0	22	CAB	−3.3% at 12 mo	L spine
Italy ²¹	M0	35	GnRH agonist	−2.3% at 12 mo	L spine
Spain ²²	M0	31	GnRH agonist	−4.8% at 12 mo	L spine
Australia ²³	M0	72	CAB	−1.9% at 9 mo −3.3% at 9 mo	Hip spine
Present study	M0 & M1	234 70	CAB GnRH agonist	−2.6% at 12 mo −4.4% at 12 mo	L spine L spine

Table 5. Prospective studies of bone mineral density (BMD) during androgen deprivation therapy (ADT).

FRAX[®] has not been validated yet; hence, a Japanese database was used instead to predict the probability of bone fracture score because of the shared similarities of racial and genetic demographics between Koreans and Japanese. Thirdly, serum testosterone level was not measurable at the time of ADT start or 12M post-ADT, which was important data related to BMD of patients. Lastly, <20% of subjects with metastasis included could be confounding factors for BMD changes by ADT. Fifth, some differences in baseline characteristics such as prostate volume, clinical nodal stage, and exercise activity, which are known to be associated with the prevalence of osteoporosis, might be underlying confounding factors that were not addressed in this study. However, all information obtained from the enrolled patients might predictably indicate that the CAB and GnRH groups would not show large baseline differences in parameters related to the prevalence of osteoporosis.

However, this study was clinically meaningful due to its study design as the first prospective study of BMD change and the fracture risk during the first 12 months ADT in Asian patients, and as the first detailed information about the clinical practice of ADT in Korean Urology, which can potentially be utilized as a reference in prostate cancer patients receiving ADT. This study identified that in cases of metastatic disease, Korean urologist's preference for ADT at a university hospital was CAB rather than GnRH agonist monotherapy for improving overall survival, as well as palliation^{4–6}. Despite the small proportion of patients with metastatic disease who were recruited in this study, many urologists selected CAB rather than GnRH agonist monotherapy for treatment, which resulted in failure to recruit sufficient subjects in the GnRH group.

Conclusions

A significant decrease of BMD was observed by 12 months ADT and no difference in BMD loss was found between the 2 groups. In particular, there was no clinical significance in terms of increased fracture by 12 months ADT. Based on these results, there are no safety concerns of bone-related diseases caused by additional bone loss with CAB. In addition, the data collected in this study can potentially be utilized as a reference in patients with prostate cancer receiving ADT.

References

- Hsing, A. W. & Devesa, S. S. Trends and patterns of prostate cancer: what do they suggest? *Epidemiol. Rev.* **23**, 3–13 (2001).
- Park, S. K. *et al.* Rising prostate cancer rates in South Korea. *Prostate*. **66**, 1285–1291 (2006).
- Oh, C. M. *et al.* Cancer statistics in Korea: incidence, mortality, survival and prevalence in 2013. *Cancer Res. Treat.*, doi: 10.4143/crt.2016.089 (2016).
- Bennett, C. L. *et al.* Maximum androgen-blockade with medical or surgical castration in advanced prostate cancer: a meta-analysis of nine published randomized controlled trials and 4128 patients using flutamide. *Prostate Cancer Prostatic Dis.* **2**, 4–8 (1999).
- Crawford, E. D. *et al.* A controlled trial of leuprolide with and without flutamide in prostatic carcinoma. *N. Engl. J. Med.* **321**, 419–424 (1989).
- Denis, L. J. *et al.* Maximal androgen blockade: final analysis of EORTC phase III trial 30853. EORTC Genito-Urinary Tract Cancer Cooperative Group and the EORTC Data Center. *Eur. Urol.* **33**, 144–151 (1998).
- Higano, C. S. Androgen-deprivation-therapy-induced fractures in men with nonmetastatic prostate cancer: what do we really know? *Nat. Clin. Pract. Urol.* **5**, 24–34 (2008).
- Kwon, T. *et al.* Bone mineral density in prostate cancer: a comparative study of patients with prostate cancer and healthy controls using propensity score matching. *Urology*. **83**, 385–392 (2014).
- Cheung, A. S., Zajac, J. D. & Grossmann, M. Muscle and bone effects of androgen deprivation therapy: current and emerging therapies. *Endocr. Relat. Cancer*. **21**, R371–R394 (2014).
- Van Hemelrijck, M. *et al.* Mortality following hip fracture in men with prostate cancer. *PLoS One*. **8**, e74492 (2013).
- Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. *World Health Organ. Tech. Rep. Ser.* **843**, 1–129 (1994).
- Smith, M. R., Fallon, M. A. & Goode, M. J. Cross-sectional study of bone turnover during bicalutamide monotherapy for prostate cancer. *Urology*. **61**, 127–131 (2003).
- Shahinian, V. B., Kuo, Y. F., Freeman, J. L., Orihuela, E. & Goodwin, J. S. Increasing use of gonadotropin-releasing hormone agonists for the treatment of localized prostate carcinoma. *Cancer*. **103**, 1615–1624 (2005).

14. Diamond, T., Campbell, J., Bryant, C. & Lynch, W. The effect of combined androgen blockade on bone turnover and bone mineral densities in men treated for prostate carcinoma: longitudinal evaluation and response to intermittent cyclic etidronate therapy. *Cancer*. **83**, 1561–1566 (1998).
15. Eriksson, S., Eriksson, A., Stege, R. & Carlström, K. Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. *Calcif. Tissue Int.* **57**, 97–99 (1995).
16. Mailefert, J. F. *et al.* Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. *J. Urol.* **161**, 1219–1222 (1999).
17. Daniell, H. W. *et al.* Progressive osteoporosis during androgen deprivation therapy for prostate cancer. *J. Urol.* **163**, 181–186 (2000).
18. Mittan, D. *et al.* Bone loss following hypogonadism in men with prostate cancer treated with GnRH analogs. *J. Clin. Endocrinol. Metab.* **87**, 3656–3661 (2002).
19. Hamilton, E. J. *et al.* Structural decay of bone microarchitecture in men with prostate cancer treated with androgen deprivation therapy. *J. Clin. Endocrinol. Metab.* **95**, E456–E463 (2010).
20. Smith, M. R. *et al.* Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. *N. Engl. J. Med.* **345**, 948–955 (2001).
21. Berruti, A. *et al.* Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J. Urol.* **167**, 2361–2367, discussion 2367 (2002).
22. Morote, J. *et al.* Bone mineral density changes in patients with prostate cancer during the first 2 years of androgen suppression. *J. Urol.* **175**, 1679–1683, discussion 1683 (2006).
23. Spry, N. A. *et al.* Long-term effects of intermittent androgen suppression on testosterone recovery and bone mineral density: results of a 33-month observational study. *BJU Int.* **104**, 806–812 (2009).
24. Morgans, A. K. *et al.* Racial differences in bone mineral density and fractures in men receiving androgen deprivation therapy for prostate cancer. *J. Urol.* **187**, 889–893 (2012).
25. George, A. *et al.* Racial differences in bone mineral density in older men. *J. Bone Miner. Res.* **18**, 2238–2244 (2003).
26. Morrison, B. F. *et al.* Bone mineral density in Jamaican men on androgen deprivation therapy for prostate cancer. *Infect. Agent Cancer* **6**, S7 (2011).
27. Wang, W. *et al.* Bone mineral density in Japanese prostate cancer patients under androgen-deprivation therapy. *Endocr. Relat. Cancer* **15**, 943–952 (2008).
28. Yuasa, T. *et al.* Relationship between bone mineral density and androgen-deprivation therapy in Japanese prostate cancer patients. *Urology* **75**, 1131–1137 (2010).
29. Deng, J. H., Yang, L. P., Wang, L. S. & Zhou, D. F. Effect of androgen deprivation therapy on bone mineral density in prostate cancer patients. *Asian J. Androl.* **6**, 75–77 (2004).
30. Kim, S. O., Kang, T. W., Kwon, D., Park, K. & Ryu, S. B. Risk factors for bone loss with prostate cancer in Korean men not receiving androgen deprivation therapy. *Int. Braz. J. Urol.* **35**, 183–188, discussion 189 (2009).
31. Melton, L. J. 3rd *et al.* Fracture risk in men with prostate cancer: a population-based study. *J. Bone Miner. Res.* **26**, 1808–1815 (2011).
32. Shahinian, V. B., Kuo, Y. F., Freeman, J. L. & Goodwin, J. S. Risk of fracture after androgen deprivation for prostate cancer. *N. Engl. J. Med.* **352**, 154–164 (2005).
33. Lassemlante, A. C., Doi, S. A., Hooper, J. D., Prins, J. B. & Wright, O. R. Prevalence of osteoporosis in prostate cancer survivors: a meta-analysis. *Endocrine* **45**, 370–381 (2014).
34. Watts, N. B., Lewiecki, E. M., Miller, P. D. & Baim, S. National Osteoporosis Foundation 2008 Clinician's Guide to Prevention and Treatment of Osteoporosis and the World Health Organization Fracture Risk Assessment Tool (FRAX): what they mean to the bone densitometrist and bone technologist. *J. Clin. Densitom.* **11**, 473–477 (2008).
35. Fujiwara, S. *et al.* Development and application of a Japanese model of the WHO fracture risk assessment tool (FRAX). *Osteoporos. Int.* **19**, 429–435 (2008).

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Additional Information

Supplementary information accompanies this paper at <http://www.nature.com/srep>

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