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ORIGINAL RESEARCH

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The relationship between serum testosterone and bone mineral density in Japanese men and the effects zoledronic acid in prostate cancer patients with low serum testosterone

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Abstract

Although hormone therapy is definitely beneficial for patients with prostate cancer, a decrease in bone mineral density and an increased risk of fracture have been noted as adverse events. Improving bone metabolism in these patients is especially important in an aging society. We herein report the results of two studies: the first examined the effect of low serum testosterone levels on bone mineral density in a large number of Japanese men; the second study investigated the effect of a 12-month formulation of zoledronic acid injection for multiple years in prostate cancer patients with castration levels of serum testosterone due to androgen deprivation therapy. The first study included 1112 patients with late-onset hypogonadism. A multiple regression analysis that included factors that were significant in the simple regression analysis showed that only age ($p < 0.001$) and testosterone ($p = 0.013$) were significantly associated with bone mineral density. A significant relationship between serum testosterone and bone mineral density was also found in an age-adjusted regression analysis ($p = 0.008$) and a trend analysis (Ptrend = 0.001). The second study included 12 prostate cancer patients with castration levels of serum testosterone due to androgen deprivation therapy, and who had received a 12-month formulation of zoledronic acid injection for multiple years. A trend analysis clearly showed that bone mineral density tended to increase year by year during the 4-year observation period (Ptrend < 0.001). In addition, we found no treatment-related adverse events in patients who received long-acting zoledronic acid. Thus, we conclude that men with lower serum testosterone levels are likely to have reduced bone mineral density and wish to emphasize that bone mineral density can be increased in prostate cancer patients by the continuous administration of long-acting zoledronic acid at 12-month intervals, even when their serum testosterone levels are below castration level.

Keywords

Testosterone; Bone mineral density; Late-onset hypogonadism; Prostate cancer; Castration level; Long-acting zoledoronic acid; Four years

1. Introduction

In 2018, 1,276,106 new cases of prostate cancer were registered worldwide, making it the second most frequent malignancy in men, representing 7.1% of all cancers in men and accounting for 3.8% of all cancer-related deaths in men [1, 2]. Basically, the treatment plan for prostate cancer depends on the stage, age, general condition of the patient, and the risk classification of the disease. Androgen deprivation therapy (ADT) has been used for patients with prostate cancer whose cancer has spread too far to be cured by radical treatment, such as surgery or radiation therapy, or who come back after such initial treatments and who cannot receive these treatments for other reasons. Regarding Japanese patients, a retrospective analysis using the database on the Japan Study Group of Prostate Cancer actually showed that combined androgen blockade (CAB) is effective in prostate cancer patients with metastasis [3]. Another study using the same database also showed that the expected survival of patients with localized prostate cancer treated by ADT is almost the same as that of the general population [4]. Indeed, in Japan, it is not clinically uncommon for ADT to be performed even in patients with localized cancer. One of the reasons for the high frequency at which ADT is selected in Japan is that ADT is more effective for Japanese men than for American and European men [5]. However, its side effects and compli-

cations have gained increased attention where ADT/CAB is used relatively frequently. According to the guidelines of the Japanese Urological Association, ADT/CAB can induce a decrease in the sexual function, including libido and the erectile function, and to exacerbate metabolic factors, such as glucose and lipid metabolism and the accumulation of body fat [6]. In addition, low serum testosterone levels due to ADT/CAB may contribute to atherosclerosis and may therefore be a risk factor for cardiovascular events. We have already reported that the number of metabolic factors (obesity, hyperglycemia, hyperlipidemia, and hypertension) is associated with lower serum testosterone levels in men undergoing health examinations and that lower testosterone levels increase the risk of developing metabolic syndrome. We also reported that low serum testosterone levels may contribute to atherosclerosis in Japanese men. Furthermore, decreased bone mineral density (BMD) and an increased risk of fracture are also well known as adverse events of ADT/CAB. In other words, the decrease in BMD due to ADT/CAB is one of the diseases referred to as cancer treatmentinduced bone loss (CTIBL) [7]. Of course, it is impossible to administer hormone replacement therapy to patients undergoing ADT/CAB with the goal of lowering serum testosterone to castration levels. For such patients treated with ADT/CAB, alendronate, risedronate, pamidronate and zoledronate were recommended as treatment options to prevent decreased BMD [8]. The clinical practice guidelines for bone health in cancer published by the European Society for Medical Oncology also recommended denosumab and bisphosphonate therapy for such patients [9]. However, it is also well known that the adherence to these medications for bone health is very low [10]. Therefore, drugs that allow longer dosing intervals, which would increase compliance, have been desired. One such drug is zoledronic acid, which can be administered intravenously every 12 months [11].

The purpose of this study was to demonstrate in a Japanese study that BMD is reduced when serum testosterone levels are low and to explore whether there are effective therapies to restore BMD even in patients with extremely low testosterone levels. Thus, in the present study, we first confirmed that serum testosterone levels are correlated with BMD in patients with symptoms of late-onset hypogonadism (LOH). Finally, patients undergoing ADT/CAB for prostate cancer were followed for 4 years to determine the effects of treatment with a 12-month intravenous formulation of zoledronic acid on BMD.

2. Patients and methods

This study on the relationship between serum testosterone and BMD included 1112 men who visited our hospital or affiliated clinic symptoms of LOH (*e.g.*, lethargy, general fatigue, malaise, depression, insomnia, frustration, reduced concentration, sweating, hot flashes, coldness, tinnitus, headache, numbness, dizziness, stiff shoulder, night sweats, erectile dysfunction and decreased libido) between November 2014 and April 2018. Their age was 50.3 ± 10.3 years, and the distribution was shown in Fig. 1. Blood samples were collected between 09:00 and 11:00, and serum testosterone levels were measured by radioimmunoassay. An ultrasound bone densitometer (Benus evo, NIHON KOHDEN, Japan) was used to quantitatively measure heel BMD according to the instructions as part of the screening examinations for LOH. This bone densitometer uses both ultrasonic pulse reflection and ultrasonic pulse transmission methods to measure the sound velocity of the calcaneus alone by measuring the reflection distance to the bone, thereby excluding the fleshy material around the calcaneus. Furthermore, by excluding changes in sound

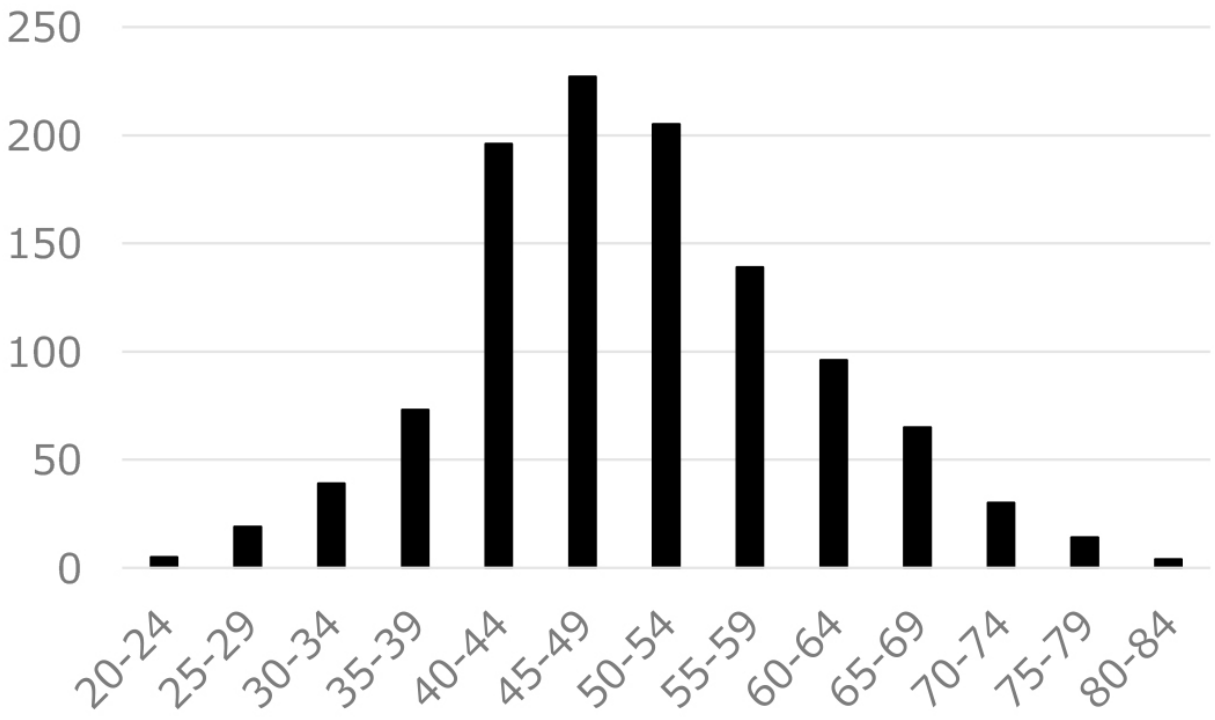

FIGURE 1. Age distribution of our patients with symptom of late onset hypogonadism.

velocity due to temperature changes in the balloon coupling area, this bone densitometer allows for more reproducible measurements and can be easily used for outpatients. BMD is presented as the %young adult mean (YAM) value. Patients with open wounds, fractures, skin inflammation around the heel or the presence of metal components in the heel were excluded from the study. Simple and multiple regression analyses and a trend analysis were performed to examine the relationship between serum testosterone and the %YAM value of BMD.

The main part of this study included 12 prostate cancer patients whose serum testosterone levels had been reduced to castration levels by ADT/CAB and who had been continuously treated with a 12-month intravenous formulation of zoledronic acid for multiple years. All patients had decided to start treatment with zoledronic acid according to the Japanese management manual for CTIBL. For these patients, BMD was measured by dual-energy X-ray absorptiometry. We evaluated the average BMD using both anterior and posterior aspects at lumbar spine levels L2–4. The data from cases with significant vertebral body deformation or $\geq$1.0 SD (standard deviation) difference between adjacent vertebral bodies were eliminated. BMD was evaluated before treatment with zoledronic acid. Thereafter, zoledronic acid was administered every 12 months, and BMD was repeatedly measured at the same time.

3. Statistical analysis

Continuous variables are expressed as the mean $\pm$ SD. A simple regression analysis was used to assess the relationship between the %YAM value of BMD and several factors, including age, blood biochemical values and hormone data in patients with LOH symptoms. If red blood cell count (RBC), hematocrit, and hematocrit, indicators of general blood tests; aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transpeptidase (γ-GTP), indicators of liver function; and cholesterol and triglyceride, indicators of lipid metabolism, were found to be factors affecting BMD, only one item in any of the indices would be used for further analysis. This is because it is assumed that each is closely related to the other. Furthermore, there are also factors that are assumed to be related to BMD, such as exercise, sleep, and daily habits including diet, but we were not able to fully understand the details in this study, so they were not included in the analysis factors. Factors that showed a statistically significant association with %YAM in a simple regression analysis were also evaluated by a multiple regression analysis to clarify the factors that were actually associated with %YAM. Finally, after classifying the patients into five groups according to their serum testosterone levels ($\leq$3.5, 3.6–4.4, 4.5–5.4, 5.5–6.6 and $\geq$6.7 ng/mL), the association of the serum testosterone level with the %YAM value of BMD was assessed by a trend analysis after adjustment for statistically significant factors identified by a multiple regression analysis. For patients whose serum testosterone level had been reduced to castration levels by ADT/CAB, the treatment effect of zoledronic acid was also evaluated by calculating the measured %YAM values as 100% of the respective pretreatment value by a trend analysis. Statistical significance was set at $p < 0.05$. All statistical analyses were performed with SPSS version 24.0 (SPSS Inc., Chicago, IL, USA).

4. Results

For the first study, the characteristics of the 1112 patients are summarized in Table 1. Their age, %YAM value of BMD and serum testosterone level were 50.3 $\pm$ 10.3 years, 92.8 $\pm$ 10.7% and 5.1 $\pm$ 1.9 ng/mL, respectively. Statistically significant factors associated with %YAM value by a simple regression analysis were age ($p < 0.001$), testosterone ($p = 0.003$), RBC ($p < 0.001$), hemoglobin ($p = 0.009$), hematocrit ($p = 0.002$), albumin ($p = 0.002$), AST ($p = 0.008$), γ-GTP ($p = 0.023$) and dehydroepiandrosterone sulfate (DHEA-S; $p = 0.047$) (Table 2). After excluding RBC count, hematocrit and AST due to the confounding effects with regard to hemoglobin and γ-GTP, a multiple regression analysis that included factors that showed statistical significance in the simple regression analysis showed that age ($p < 0.001$) and testosterone ($p = 0.013$) were the only factors that remained significantly associated with the %YAM value of BMD (Table 3). Furthermore, a significant relationship between testosterone and the %YAM value of BMD was found in the age-adjusted regression analysis (regression coefficient, 0.442; $p = 0.008$). In a trend analysis adjusted for age, serum testosterone levels were significantly related to BMD in patients with LOH symptoms (Ptrend = 0.001; Fig. 2). This means that men with lower serum testosterone levels are likely to have reduced BMD.

The characteristics of 12 patients who were included in the study on the efficacy of zoledronic acid are summarized in Table 4. The mean age was 80.2 $\pm$ 6.5 years. All patients were treated with goserelin or leuprorelin as ADT, and 9 patients also took bicalutamide. Three participants were diagnosed with osteoporosis based on a %YAM value of $<$70, and others had a past or family history of pathological fracture. The effect of the intravenous administration of zoledronic acid every 12 months is shown in Fig. 3. The %YAM value of BMD before the administration of zoledronic acid was set at 100, and the relative change after treatment was expressed in years. A trend analysis clearly showed that the %YAM value of BMD tended to increase year by year during the 4-year observation period (Ptrend $<$ 0.001). In addition, no treatment-related adverse events were observed in this period.

5. Discussion

We report on two studies. The first examined the effect of low serum testosterone levels on BMD in a large number of cases, along with various other factors that could be expected to be associated with such a decrease. Historically, low serum estrogen was first shown to be associated with BMD, but eventually the importance of testosterone with respect to bone metabolism also became apparent. Osteocytes and osteoblasts, which are activated by testosterone and its metabolite dihydrotestosterone *via* the androgen receptors, bring anabolic interaction to bone. Moreover, testosterone is involved in osteoblast proliferation by indirectly changing receptor activator of nuclear factor-kappa B ligand (RANKL). A large-scale study that included 2908 elderly men (mean age: 75.4 years) reported

TABLE 1. Clinical characteristics of 1112 patients with late onset hypogonadism.

Characteristics	Mean ± SD	95% CI
Age (yr)	50.3 ± 10.3	(22–86)
%YAM value (%)	92.8 ± 10.7	(47–166)
Testosterone (ng/mL)	5.1 ± 1.9	(0.3–14.6)
RBC ($\times 10^6$/mL)	483.6 ± 40.6	(238–612)
Hemoglobin (g/dL)	15.0 ± 1.1	(9.1–19.6)
Hematocrit (%)	45.2 ± 3.2	(27.4–57.2)
Triglyceride (mg/dL)	129.9 ± 159.2	(22–3556)
T-Cholesterol (mg/dL)	205.0 ± 35.1	(89–546)
Total protein (g/dL)	7.4 ± 0.4	(5.1–9.3)
Albumin (g/dL)	4.6 ± 0.3	(2.0–5.5)
AST (U/L)	25.7 ± 16.6	(10–312)
ALT (U/L)	29.2 ± 22.5	(6–221)
γ-GTP (U/L)	54.7 ± 81.4	(10–1254)
Creatinine (mg/dL)	0.9 ± 0.3	(0.5–6.4)
FBS (g/dL)	95.5 ± 22.1	(62–386)
DHEA-S (μg/dL)	220.2 ± 102.2	(15–741)
Cortisol (μg/dL)	9.6 ± 3.7	(0.8–15.6)
IGF-1 (ng/mL)	138.1 ± 39.6	(41–393)

YAM: young adult mean; RBC: red blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GTP: glutamyl transpeptidase; FBS: fasting blood sugar; DHEA-S: dehydroepiandrosterone sulfate; IGF-1: insulin-like growth factor 1; SD: standard deviation; CI: confidence interval.

TABLE 2. Simple regression analysis of the association between %YAM of BMD and various factors.

	Regression coefficient	*p*	95% CI	
			Lower	Upper
Age	−0.213	<0.001	−0.275	−0.150
Testosterone	0.533	0.003	0.171	0.835
RBC	0.031	<0.001	0.015	0.047
Hemoglobin	0.757	0.009	0.189	1.325
Hematocrit	0.329	0.002	0.122	0.535
Triglyceride	<0.001	0.959	−0.004	0.004
T-Cholesterol	−0.005	0.583	−0.024	0.013
Total protein	−0.027	0.976	−1.753	1.699
Albumin	3.569	0.002	1.319	5.819
AST	−0.033	0.008	−0.072	0.005
ALT	−0.013	0.362	−0.042	0.015
γ-GTP	−0.009	0.023	−0.017	−0.001
Creatinine	−2.381	0.051	−4.776	0.014
FBS	−0.029	0.067	−0.060	0.002
DHEA-S	0.006	0.047	0.000	0.013
Cortisol	0.162	0.069	−0.013	0.388
IGF-1	0.053	0.345	−0.058	0.165

YAM: young adult mean; BMD: bone mineral density; RBC: red blood cell; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GTP: glutamyl transpeptidase; FBS: fasting blood sugar; DHEA-S: dehydroepiandrosterone sulfate; IGF-1: insulin-like growth factor 1; CI: confidence interval.

TABLE 3. Multiple regression analysis of the association between %YAM of BMD and various factors.

	Regression coefficient	*p*	95% CI	
			Lower	Upper
Age	−0.206	<0.001	−0.278	−0.133
Testosterone	0.429	0.013	0.090	0.768
Hemoglobin	0.359	0.240	−0.240	0.957
Albumin	1.666	0.197	−0.864	4.196
γ-GTP	−0.008	0.051	−0.016	0.000
DHEA-S	−0.005	0.169	−0.012	0.002

YAM: young adult mean; BMD: bone mineral density; GTP: glutamyl transpeptidase; DHEA-S: dehydroepiandrosterone sulfate; CI: confidence interval.

that serum testosterone and estrogen were strong predictors of BMD at all bone sites [12]. Another study that included 3875 middle-aged men (20–59 years) also showed a positive association between serum testosterone and the lumbar BMD [13]. In fact, the prevalence of osteoporosis increased up to 40% in patients with Klinefelter syndrome, a typical chromosomal abnormality associated with low serum testosterone levels due to testicular atrophy. However, to date there have been no large-scale studies of the relationship between serum testosterone and BMD in the Japanese population. Thus, we first investigated this relationship among more than 1000 men with various symptoms of LOH. The average age of our patients was 50.3 years (range: 22 to 86 years). Simple and multiple regression analyses, including various factors, revealed that age and serum testosterone were the only factors associated with the %YAM value of BMD. Furthermore, the significant relationship between serum testosterone and %YAM remained after adjustment for age. In fact, when examining serum testosterone in five classifications, it was clear that the %YAM value of BMD gradually decreased as the serum testosterone level decreased (Fig. 2). As a previous study pointed out [13], strategies that increase testosterone levels may have good potential to improve skeletal health in middle-aged men with low serum testosterone levels. However, this strategy is impossible to apply to patients with prostate cancer.

ADT is well known to reduce BMD by 5–10% in the first year of treatment. Furthermore, the risk of pathological fracture increases to 19.4% in prostate cancer patients treated with ADT for five years; in contrast, the risk is approximately 12.6% in prostate cancer patients without ADT [14]. This risk of fracture in elderly men is directly related to frailty,

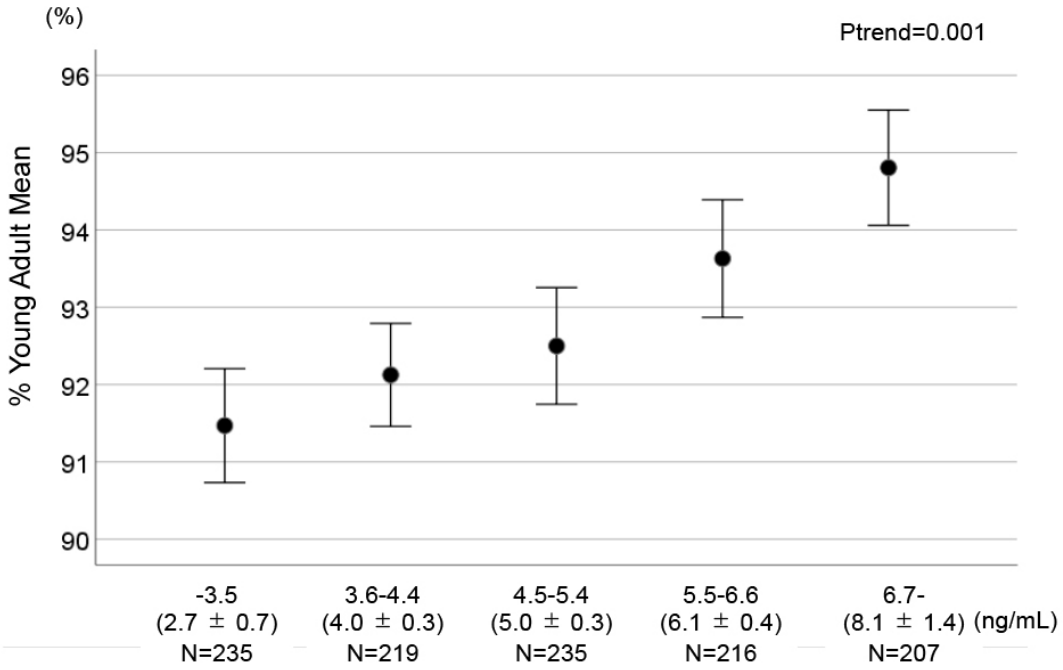

FIGURE 2. Trend analysis between serum testosterone and the %young adult mean of bone mineral density after classifying the patients into five groups according to their serum testosterone levels (Ptrend = 0.001).

TABLE 4. Clinical characteristics of 12 prostate cancer patients treated with a 12-month intravenous formulation of zoledronic acid.

Patient	Age	Whitmore-Jewett staging	D'Amico classification	Gonadotropin-releasing hormone agonist	Bicalutamide
1	86	D1	Very high	Goserelin	+
2	87	B1	High	Leuprorelin	-
3	78	D2	High	Leuprorelin	+
4	67	B1	Intermediate	Leuprorelin	-
5	79	B0	High	Goserelin	+
6	84	B1	Intermediate	Leuprorelin	+
7	82	B2	Intermediate	Leuprorelin	+
8	80	B1	Intermediate	Leuprorelin	+
9	88	B2	High	Goserelin	+
10	81	C1	Very high	Goserelin	+
11	81	B0	Intermediate	Leuprorelin	-
12	69	B1	Intermediate	Goserelin	+

which has recently received much attention, and its prevention is now considered important. Several drug treatments have been developed for decreased BMD and osteoporosis. In patients with a decrease in BMD as a result of CTIBL in association with ADT/CAB, if the patient is deemed to be amenable to treatment, therapeutic agents should be administered. In Europe and the United States, bisphosphonates and denosumab, a human monoclonal antibody against RANKL, have been investigated as the treatment of choice for CTIBL, with favorable results reported for zoledronic acid in particular [15]. In Japan, good results with zoledronic acid [16, 17] and denosumab have also been reported for such patients [18]. In prostate cancer patients with decreased BMD causing osteoporosis, bisphosphonates have been used clinically [19, 20]. However, these medications are associated with very low compliance, as the absence of symptoms leads to forgetting or neglecting treatment. In fact, the retention rate for patients receiving bisphosphonates is approximately 40% after starting treatment. Regarding compliance, adequate explanation of drug side effects and patient education regarding the need for continued treatment are important. Furthermore, with denosumab, higher continuation rates have been reported for formulations that can be administered weekly in comparison to those that are administered daily; the same has been reported for formulations that can be administered once a month in comparison to those that are administered once a week [21].

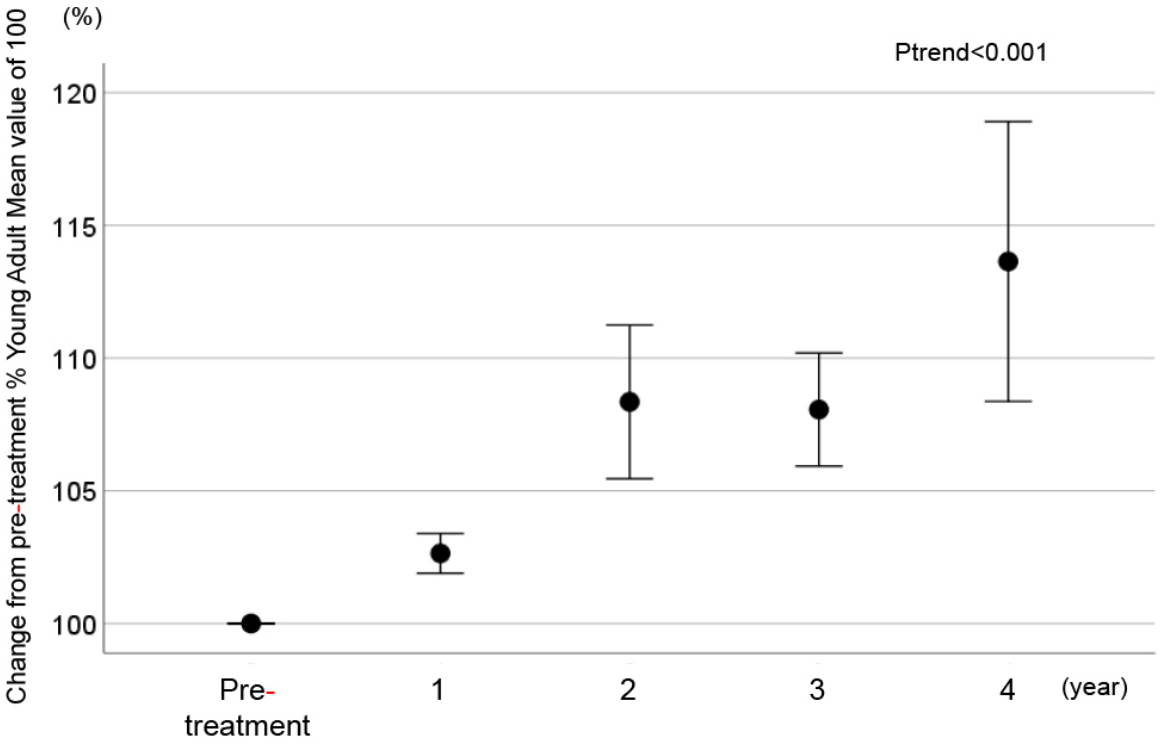

FIGURE 3. Trend analysis showing that the %young adult mean value of bone mineral density tended to increase with each year of treatment (Ptrend < 0.001).

Recently, long-acting zoledronic acid, the blood concentration of which can be controlled by annual administration, has been expected to improve the decrease in BMD [22]. The benefits of long-acting zoledronic acid in patients with prostate cancer undergoing ADT have been reported in several Japanese studies [23, 24]. However, these reports have only looked at changes after one year of treatment with a single administration of long-acting zoledronic acid, and there are no reports on changes in BMD when the treatment is continued year by year over multiple years. The purpose of our second study was to determine the effect of multiple doses of this 12-month continuous formulation of zoledronic acid. In this regard, we clearly showed that multiple annual doses of long-acting zoledronic acid gradually increased the %YAM value of BMD over time.

The present study was associated with some limitations. First, we conducted blood tests to determine the biochemical and endocrinological profiles only once for patients with symptoms of LOH. Such testing, especially the endocrinological profile, should be repeated clinically. It would be more accurate to use the average of multiple blood tests. Second, we could not check lifestyle factors, including smoking, alcohol consumption, sleeping status, and exercise, for those patients because of the retrospective nature of the study. Growth hormone, which promotes bone growth and development, is secreted at night, especially during deep sleep, and acts on epiphyseal cartilage to build a large and strong body. This suggests that sleep duration and BMD may be closely related, but no further information could be collected in a retrospective analysis. In addition to age and serum testosterone level, there may be other factors involved in BMD. For example, it has been speculated that patients with metabolic syndrome may have lower BMD, but the details of the association are not yet clear. Third, for patients with prostate cancer, zoledronic acid was administered for 12 months in principle, but there were some patients whose doses were delayed by approximately one month. However, it is unlikely that this would significantly affect the results. Finally, it is also an important limitation that only 12 prostate cancer patients were able to observe the effects of zoledronic acid over several years. We plan to increase the number of patients and conduct further studies in the future. Although these limitations cannot be ignored, we believe that our findings represent the relationship between serum testosterone and BMD and the efficacy of multiple doses of the 12-month continuous formulation of zoledronic acid for prostate cancer patients whose serum testosterone level had been reduced to castration levels by ADT/CAB.

6. Conclusions

In conclusion, although continuous follow-up of BMD is necessary, we emphasize that the continuous administration of long-acting zoledronic acid at 12-month intervals can increase BMD in prostate cancer patients with serum testosterone levels below castration levels.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

AK, KI, KK and AT—Study conception and design. MS, YA, AT, YU and TN—Data acquisition. MS and KK—Analysis and interpretation of data. AK and AT—Drafting the article.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The procedures were approved by the Regional Ethics Committee of Juntendo Urayasu Hospital, Urayasu, Japan (approval numbers: 2018-029 and E22-0480-U01). Informed consent was obtained from all participants in the study.

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CONFLICT OF INTEREST

The authors declare no conflict of interest. Akira Tsujimura is serving as one of the Editorial Board members of this journal. We declare that Akira Tsujimura had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to KSH.

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