

## EFFECT OF ANDROGEN SUPPRESSION ON BONE MINERAL DENSITY IN PATIENTS WITH PROSTATE CANCER

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The androgen-suppressive therapy (AST) in patients with prostate cancer (PC) may dramatically affect the bone mineral density (BMD), which puts patients at risk of severe adverse effects, such as weight-bearing bone fractures. *Aim:* To study the effect of AST on BMD in patients with non-metastatic hormone-sensitive PC treated with intermittent hormonal therapy, and effect of different total testosterone level on BMD. *Materials and Methods:* From 2011 to 2013 we treated 56 patients with non-metastatic hormone-naïve PC. Intermittent hormonal treatment with flutamide at a dose of 250 mg 3 times per day with nine monthly injections of luteinizing gonadotropin releasing hormone (LGNRH) [“treatment” period] followed by period of observance (“no treatment”) was administered. We evaluated the BMD of lumbar spine and both proximal thighs by means of dual-energy x-ray densitometry at the end of “treatment” period and at the end of “no treatment” period. *Results:* During the first treatment period, 44 of 56 patients (78.6%) experienced the reduction in BMD in both lumbar spine and thighs. Total testosterone level in all patients dropped to castration level. During the first period of “no treatment” there was an increase in BMD ( $p < 0.05$ ) in 30 (68.2%) of 44 patients. The median time to recovery of total testosterone level to the level  $> 50$  ng/dl was 91 days (from 30 to 308 days), and  $> 100$  ng/dl was 110 days (from 49 to 343 days). The changes in BMD positively correlated with the changes in total testosterone level (correlation 0.18 [95% CI, 0.04–0.27],  $p = 0.009$ ). The decline in total testosterone level in serum was followed by the decline in BMD value in the studied areas, and *vice versa*. *Conclusions:* The changes in BMD positively correlated with changes in total testosterone level. The BMD decreases during the androgen suppression and increases during the pause in the treatment. This demonstrates the benefit of intermittent AST in preventing osteoporosis, pathological bone fractures and possibly, bone metastases. *Key Words:* prostate cancer, hormone therapy, osteoporosis, bone mineral density.

Androgen-suppressive therapy (AST), which is achieved by performing bilateral orchiectomy, administration of agonists or antagonists of luteinizing gonadotropin releasing hormone (LGNRH) is widely used in the treatment of prostate cancer (PC) [1]. Long-term AST may cause side effects, such as hot flashes, sexual dysfunction, hyperlipidemia, increased risk of heart attack, etc. [2, 3]. AST may also lead to reduction in bone mineral density (BMD), which increases the risk of osteoporosis and bone fractures [4]. Admission of AST longer than 1 year increases the rate of BMD loss by 5–10 times and, consequently, the risk of fractures [5]. The efficacy of intermittent AST compared with continuous AST showed similar results in cancer-specific and overall survivals [6, 7]. Intermittent AST reduces the frequency of hot flashes and erectile dysfunctions, but lacks the data about the impact on BMD and fracture prevention [8].

We explored short-term changes in BMD over the course of intermittent AST in men with nonmetastatic hormone-sensitive PC.

### MATERIALS AND METHODS

During November 2011 to December 2013 we treated 56 patients with non-metastatic hormone-sensitive PC.

All patients were administered intermittent AST. The patients were classified as per D’Amico [9] as PC patients with mild to moderate risk of progression (total prostate-specific antigen [PSA]  $< 20$  ng/ml, the Gleason score  $\leq 7$ ). The study was approved by the Bioethics Committee of SE “Institute of Urology of National Academy of Medical Sciences of Ukraine”. All patients signed informed consent to participate in the study. The study group also included patients with biochemical recurrence of PC after radical prostatectomy or external beam radiation therapy (EBRT). The level of PSA was determined in serum by enzyme immunoassay test. All patients underwent bone scan (BS), computed tomography (CT) of chest, abdomen and pelvis, and bone densitometry by means of dual-energy x-ray absorptiometry (DEXA). The metastatic disease was ruled out by BS and CT. The BMD was determined on DEXA by scanning the lumbar spine and both proximal thighs using densitometer “Prodigy” GE, Lunar. The study included measurement of two variables: 1. Projected square of the investigated area, in  $\text{cm}^2$  (area). 2. Bone mineral content of the given square, in g (BMD). The clinically important parameter projected BMD (BMD/area) was calculated using these two values and was expressed in  $\text{g}/\text{cm}^2$ . The degree of reduction in BMD was assessed by the T-score according to the WHO classification [10]. T-score is the difference between the bone density of a particular patient and the mean density of young healthy adult in the age prior to the loss of bone density in people of the same sex. Results are expressed

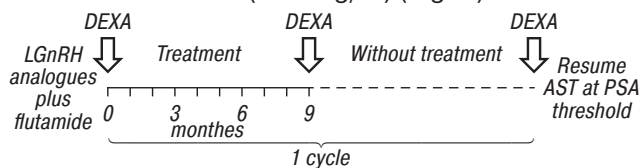
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*Abbreviations used:* AST – androgen-suppressive therapy; BMD – bone mineral density; CT – computer tomography; DEXA – dual-energy x-ray absorptiometry; EBRT – external beam radiation therapy; LGNRH – luteinizing gonadotropin releasing hormone; PC – prostate cancer; PSA – prostate specific antigen; RBS – radionuclide bone scan.

in standard deviations (SD). Normal BMD is within one SD of the young adult mean ( $T > -1.0$ ). Decreased bone density (osteopenia) is observed at the value of BMD between  $-1.0$  and  $-2.5$  SD [ $T = (-1.0) - (-2.5)$ ]. A DEXA T-score less than or equal to  $-2.5$  SD from the mean peak bone mass ( $T \leq -2.5$ ) is considered osteoporosis. Using the DEXA results all patients were split into groups with osteopenia and osteoporosis according to decreased T-score in at least one of the examined areas of the skeleton (lumbar spine, both proximal thighs) as per appropriate standards of WHO [10].

The patients were administered 9 months of AST (flutamide + LGnRH). After 9 months of the treatment BS, CT and DEXA were done. AST was stopped when reached the PSA nadir of  $\leq 4$  ng/ml. When PSA value was enhanced above predetermined threshold ( $PSA > 1$  ng/ml for patients after radical prostatectomy, and  $PSA > 4$  ng/ml for patients after EBRT or AST monotherapy), we administered new course of hormonal treatment and repeated the baseline assessments. We measured PSA total and total testosterone monthly. Each cycle of therapy included 9-months period of hormonal treatment followed by variable period of “no treatment”, length of which depended on the growth of PSA above the predetermined threshold. All patients were on AST until the signs of hormonal resistance, which was defined by three consecutive increases in PSA when the total testosterone level was at the castrate level ( $< 20$  ng/dl) (Fig. 1).



**Fig. 1.** The full cycle of intermittent AST

The absolute change and percentage change of initial average BMD compared with subsequent DEXA measurements were estimated in patients during “treatment” and “no treatment” periods. The correlation between BMD and total testosterone level was evaluated with use of Pearson correlation coefficient.

**RESULTS**

The mean age of patients was 64.5 years (from 49.8 to 80.9 years). Depending on the type of treatment received, all patients were split in the following groups: AST monotherapy — 40 patients, adjuvant AST after EBRT — 13 patients, adjuvant AST after radical prostatectomy — 3 patients. The patients were divided into following groups according to BMD values of T-score:  $T > 2.5$  — 3 patients, T-score =  $1.0 - 2.5$  — 18 patients, T-score =  $0.0 - 1.0$  — 35 patients, T-score =  $(-1.0) - 0.0$  — 16 patients, T-score =  $(-2.5) - (-1.0)$  — 11 patients (Table).

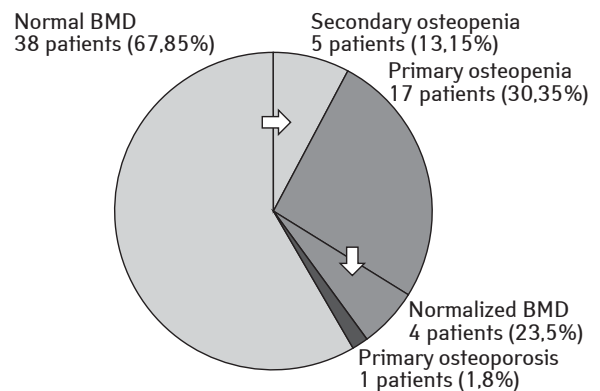
**Table.** Initial BMD (T-score)

T <sub>sp</sub>	> 2.5	1.0-2.5	0.0-1.0	-1.0-0.0	-2.5-(-1.0)
Number of patients	3	18	35	16	11

The average initial BMD T-score was  $-0.02$  (from  $-2.48$  to  $4.64$ ). There were two AST cycles completed during the study (see Fig. 1). After the first 9 months

of AST average absolute difference of BMD was  $-0.04$  g/cm<sup>2</sup> ( $p < 0.001$ ). The average relative difference in BMD after the first treatment period was  $-3.4\%$  ( $p < 0.001$ ). After the first period of the “no treatment” average absolute difference of BMD was  $0.02$  g/cm<sup>2</sup> ( $p = 0.001$ ). The average relative difference of BMD after the first “no treatment” period was  $1.4\%$  ( $p < 0.001$ ). Thus, the increase in BMD was statistically significant after the first period of “no treatment”.

During the first treatment period the decrease in BMD was observed in 44 (78.5%) of 56 patients. During the first “no treatment” period BMD grew in the examined bone areas ( $p < 0.05$ ) in 30 (66.7%) of 45 patients (Fig. 2).



**Fig. 2.** Patients with types of BMD’s violations during the treatment

38 (67.85%) among 56 patients had an initial average BMD within the normal range. 5 (13.15%) men out of 38 developed the secondary osteopenia during the treatment. The primary osteopenia was seen in 17 (30.35%) of 56 patients at the baseline. BMD returned to normal values in 4 (23.5%) of 17 patients with primary osteopenia during no AST treatment. Only 1 (1.8%) patient of 56 had primary osteoporosis. There was no pathological fractures occurred among patients who received intermittent AST over 2 years.

The median time to recovery of the total testosterone levels greater than 50 ng/dl was 91 days (from 30 to 308 days), and to the level greater than 100 ng/dl was 110 days (from 49 to 343 days). Only in 6 patients (13.3%) the total testosterone level remained stable at the castrate level during “no treatment” period. In the rest, total testosterone level was  $< 100$  ng/dl during “no treatment” period. Thus, the production of total testosterone was restored during the periods between AST in the most patients. The changes in BMD positively correlated with changes in total testosterone level (correlation 0.18 [95% CI, 0.04–0.27],  $p = 0.009$ ), which means that the increase of total serum testosterone level was followed by the increase in BMD value in the studied areas and *vice versa*.

**DISCUSSION**

In this study we presented the dynamics of changes in BMD during intermittent AST. DEXA was performed at the beginning of each treatment period and at the period of “no treatment”. This let us assess the effects of decline and growth of testosterone level on BMD values. There was no evidence of pathological frac-

tures occurred among patients receiving intermittent AST over 2 years. In patients who received continuous AST, the incidence of fractures accounted for 3.9% over 2 years [11]. This study showed that BMD was decreased during the hormonal therapy and increased during recovery of testosterone level during “no treatment” period. To maintain stable BMD in men receiving AST, and to improve BMD in patients with secondary reduction of BMD an antiresorptive therapy may be prescribed: bisphosphonates, inhibitor of RANK ligand (denosumab), anti-estrogenic drugs (toremifene), calcitonin and more [12]. Intermittent AST promotes recovery of BMD in the period of withdrawal of hormonal treatment, which may prevent the appearance of osteoporosis and prevent the administration of additional therapy. That’s why in our study the patients were not prescribed any antiresorptive medication.

Yi et al. [13] have shown in an animal model of osteoblastic metastasis that an initial phase of bone destruction is followed by extensive formation of bone. Their data suggest that bone resorption precedes bone formation in the development of osteoblastic metastases and that osteoclast activation plays an important role in the development of osteoblastic metastases. The production of testosterone is shut with continuous AST, which causes the decrease in osteoprotegerin receptor expression, and its lack accelerates bone resorption through the complex cellular mechanisms [14]. Thus, it can be postulated that intermittent AST delays the appearance of bone metastases due to the decrease in resorptive processes in skeleton.

In conclusion, we have shown that the changes in BMD positively correlated with changes in total testosterone level. The BMD decreases during the androgen suppression and increases during the pause in the treatment. This demonstrates the benefit of intermittent AST for the prevention of osteoporosis, pathological bone fractures, and, possibly, development of bone metastases.

### CONFLICT OF INTEREST

The authors declare no conflict of interest.

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