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Original Article

Effect on bone mineral density in surgical versus medical castration for metastatic prostate cancer

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ABSTRACT

Objective: This pilot study aimed to objectively assess the osteoporotic effect caused by androgen deprivation therapy (ADT) in patients with prostate cancer and compare this effect in surgical versus medical castration, specifically with luteinizing hormone-releasing hormone (LHRH) antagonists.

Material and methods: The study included 60 patients with metastatic prostate adenocarcinoma treated with either bilateral orchidectomy (group I) or LHRH antagonist (Degarelix) injection (group II). The patients had a baseline bone mineral density (BMD) assessment before the start of ADT using dual energy X-ray absorptiometry (DEXA) scan and then follow-up assessment after 6 months. BMD was measured at the spine (lumbar vertebrae L2–L4), femur (total), and forearm (one-third radius).

Results: Group I included 33 patients and group II 27 patients. Both the groups showed significant reduction in BMD at the spine and femur after 6 months, whereas the forearm did not show a significant reduction. Spine BMD showed 5.9%±2.6% and 4.7%±2.6% reduction whereas the femur BMD showed 6%±7.4% and 6%±4.7% reduction in the orchiectomy and the Degarelix groups, respectively. There was no statistically significant difference between the groups at the 3 measured sites.

Conclusion: Both surgical castration and LHRH antagonists were associated with significant accelerated osteoporotic effect at the spine and femur after 6 months without difference between both the methods. Assessment of osteoporotic risk together with preventive or management measures should be started early during ADT.

Keywords: Androgen deprivation therapy; osteoporosis; prostatic carcinoma.

Introduction

Prostate adenocarcinoma is the second most frequently diagnosed cancer in men and the fifth leading cause of cancer deaths in men worldwide.[1] Androgen deprivation therapy (ADT) is the mainstay of management of metastatic prostate cancer.[2]

Androgens have an important role in protecting bone mass in men. Although aromatization of testosterone to estradiol has a pivotal role on bone metabolism, it was demonstrated that androgens have a direct independent effect on bone mineral density (BMD) in men, both by promoting bone formation and suppression of bone resorption.[3] Androgens can stimulate proliferation of human osteoblasts and also have direct inhibiting effect on osteoclasts.[4,5]

Studies have reported that ADT is associated with accelerated osteoporosis and loss of BMD in a time-dependent manner leading to increased risk of skeletal related events (SREs).[6,7] Moreover, autopsy studies have revealed that metastatic prostate cancer is associated with bone involvement in more than 80% of cases.[8] However, most bone lesions in prostate cancer are osteoblastic in nature, and bone metastasis is associated with increased risk of developing bone complications.[9] Skeletal fractures negatively correlate with overall survival, and maintaining skeletal health is crucial for better life quality in men with prostate cancer.[10]

A dual energy x-ray absorptiometry (DEXA) scan has been established as the most widely used method to assess bone density. DEXA allows scanning of both central and peripheral

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bone density. Central bone density is assessed in lumbar spine and proximal femur, whereas the distal forearm (one-third radius) usually assesses peripheral bone density. These 3 sites, being most frequent sites of disabling osteoporosis related fractures, measure the degree of osteoporosis and predict the risk of fracture. T-score correlates the patient's BMD in relation to a young-adult reference population according to the following equation:

$$\text{T-score} = \frac{\text{Measured BMD} - \text{Young adult mean BMD}}{\text{Young adult standard deviation (SD)}}$$

According to the T-score, DEXA scan results can be classified as normal (T-score>–1), osteopenia (T-score between –1 and –2.5), or osteoporosis (T-score <–2.5).[11,12]

Assessment of BMD with a DEXA scan is generally recommended before starting long-term ADT and then yearly.[2,13,14] The European Association of Urology guidelines suggest preventive use of bisphosphonate therapy in patients with an initial low BMD (T-score <–2.5 or <–1 with other risk factors).[2]

There has been a debate in the literature about whether surgical or medical castration has more deleterious effect on BMD.[15-18] The objective of this pilot trial was to quantitatively assess early osteoporotic effect of ADT and compare this effect in surgical castration through bilateral orchiectomy and medical castration by luteinizing hormone-releasing hormone (LHRH) antagonist injection in patients with metastatic prostate cancer.

Material and methods

This prospective non-randomized pilot study was conducted on 60 patients who presented to our tertiary hospital between May 2016 and September 2018 with metastatic prostate cancer. All the patients had positive bone scans for metastasis and were counseled about all the methods of hormonal therapy and advantages and disadvantages of each. The study was conducted to compare the following 2 groups of patients:

Group I: Patients who accepted treatment by bilateral orchiectomy. Total orchiectomy was done either under general or spinal anesthesia.

Group II: Patients who accepted treatment by Degarelix (Firmagon™; Ferring Pharmaceuticals, Saint-Prex, Switzerland) injection. The starting dose was 2 injections of 120 mg (total 240 mg) and then a monthly 80 mg injection.

DEXA scan was initially performed on all the patients before starting androgen deprivation and was repeated after 6 months. As usually used for assessment of DEXA scan results, the references used for BMD measurements were L2–L4 for the lumbar spine, the total femur for the proximal femur, and one-third-radius (radius 33%) for the forearm.[12] The patients did not receive calcium or vitamin D supplements during the duration of the study. All the scans were performed using Lunar Prodigy ™ (GE Healthcare, Madison, WI, USA).

The study was approved by the ethics committee at Faculty of Medicine, Alexandria University (April 2016).

Statistical analysis

The Monte Carlo correlation test was used to determine a significant relationship between nominal/categorical variables, and the Student's t-test or paired t-tests were used for ordinal/continuous variables. The p value for statistical significance was set at $p<0.05$.

Main Points:

- Osteoporotic effect is one of the major adverse events of androgen deprivation therapy.
- There is a debate in the literature regarding whether bilateral orchidectomy as the standard ADT, is associated with less deleterious effect on bone mineral density (BMD) than other methods of hormonal therapy.
- We compared the osteoporotic effect of bilateral orchiectomy versus luteinizing hormone-releasing hormone (LHRH) antagonist (Degarelix) within 6 months of follow-up.
- The study showed similar significant accelerated osteoporotic effect at the spine and femur after 6 months with both methods.
- This was the first study to compare orchiectomy and LHRH antagonists in terms of effect on BMD.

Results

The study included 60 patients, of whom 33 were included in group I and 27 in group II. Table 1 shows the descriptive data of patients in both the groups.

Follow-up DEXA scan results after 6 months were compared with the initial presenting measurements. At the spine, follow-up BMD measurement after 6 months showed significant reduction ($p<0.001$) in both groups without significant difference between the groups ($p=0.342$). Spine BMD showed 5.9%±2.6% and 4.7%±2.6% reduction in the orchiectomy and Degarelix groups, respectively.

At the femur, the follow-up DEXA scan also showed significant reduction in both the groups ($p=0.009$ in group I, $p=0.003$ in group II) without significant difference between the groups ($p=0.898$). Follow-up BMD demur showed 6%±7.4% and 6%±4.7% reduction in the orchiectomy and Degarelix groups,

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Table 1. Descriptive data of patients in both groups

		Group I (n=33)	Group II (n=27)	p
Age (years) mean±SD		67.73±7.24	67.80±7.73	0.973*
Serum PSA (ng/mL) n (%)	<20	4 (12.1)	4 (14.8)	0.912**
	20–50	5 (15.2)	3 (11.1)	
	>50	24 (72.7)	20 (74.1)	
Gleason groups n (%)	Group I	6 (18.2)	2 (7.4)	0.027**
	Group II	3 (9.1)	2 (7.4)	
	Group III	6 (18.2)	15 (55.6)	
	Group IV	10 (30.3)	2 (7.4)	
	Group V	8 (24.2)	6 (22.2)	

*Student t-test. **Monte Carlo correlation test comparing between the groups. PSA: prostatic specific antigen; SD: standard deviation

Table 2. Initial and follow-up DEXA scan results in both the groups

		Group I	Group II	p*
BMD spine	Initial mean±SD	1.192±0.242	1.171±0.211	0.815
	Follow-up mean±SD	1.119±0.214	1.115±0.200	0.965
	BMD reduction, %	↓5.935±2.62	↓4.727±2.608	0.342
	p**	<0.001	<0.001	
BMD femur	Initial mean±SD	1.043±0.236	0.988±0.206	0.368
	Follow-up mean±SD	0.974±0.186	0.924±0.186	0.554
	BMD reduction, %	↓6.065±7.401	↓6.054±4.771	0.898
	p**	0.009	0.003	
BMD forearm	Initial mean±SD	0.827±0.121	0.790±0.136	0.520
	Follow-up mean±SD	0.821±0.086	0.760±0.199	0.157
	BMD reduction, %	↓0.463±12.440	↓4.476±11.276	0.471
	p**	0.807	0.277	

*Student t-test for comparing between the 2 groups. **Paired t-test for comparing between on admission and follow-up in each group. BMD: bone mineral density; SD: standard deviation

respectively. At the forearm, there was no significant reduction in BMD between the initial and follow-up measurements or between the groups (p=0.807 in orchiectomy, p=0.277 in Degarelix) as shown in Table 2.

Discussion

The adverse effect on bone health is an issue of interest with the wide use of ADT in management of advanced prostate cancer. A prospective study on 65 patients treated with LHRH agonists with 6-month follow-up by Lee et al.[19] in 2005 demonstrated a decrease in the hip BMD (1.9%±2.7%) using DEXA scan and showed that the effect increased with long-term treatment. Stoch et al.[20] in 2001 also reported similar results using both DEXA scan and ultrasound in all the measured sites; spine, hip, forearm, heel, and forearm. Yaturu et al.[21] in 2005 showed similar results on patients receiving LHRH agonists with the beneficial prophylactic role of bisphosphonate that decreased bone loss in those patients.

All the patients on ADT should be encouraged to adopt lifestyle changes to minimize BMD loss. Increased physical activity, cessation of smoking, and decreased alcohol consumption together with calcium and vitamin D supplements are recommended.[2,13]

Although deleterious effect on bone was reported in both surgical castration and medical castration, especially with LHRH agonists; there has been a conflict in the literature about whether surgical castration or LHRH agonists have a more deleterious effect on BMD. Kiratli et al.[15] in 2001 reported that surgical castration may be associated with higher risk than LHRH agonists, especially with the intermittent use of LHRH agonists.

However, some recent trials showed a more deleterious effect on BMD with medical castration, specifically LHRH agonists, than surgical castration. In 2013, Jia-Qi et al.[16] compared the metabolic complication of bilateral orchiectomy with that of LHRH agonists showing that medical castration caused more reduction of BMD in spine and hip using DEXA scan. Moreover, in 2016, Vargas et al.[17] in a prospective study concluded that LHRH agonists cause worse metabolic changes than did bilateral orchiectomy, including more risk of bone loss and osteoporosis, especially at the spine (L1–L4).

A couple of studies indirectly compared the effect on BMD by comparing the rate of SREs after long-term treatment. Both Sun et al.[22] and Van Asseldonk et al.[23] in retrospective studies showed that surgical castration was associated with lower risk of any fracture.

In contrast to multiple studies, Reis et al.[18] in 2009 studied the metabolic effects and change in body composition with bilateral orchiectomy. They showed that bilateral orchiectomy was not associated with a significant decrease of BMD within 12 months of follow-up.

To the best of our knowledge, our study was the first to compare LHRH antagonist with bilateral orchidectomy in terms of the

effect on BMD. Our results demonstrated significant reduction in BMD in spine and femur within 6 months of castration. There was no significant difference between the groups. Forearm measurements showed no significant reduction in BMD after 6 months in both the groups. The change may be insignificant in forearm measurements owing to the short duration of follow-up which may be insufficient to cause a remarkable change in the small bone of the forearm considering that 33% of the radius was considered as the reference for forearm measurement.

Our study had a few limitations, including the small number of patients, short-term follow-up, and a lack of correlation of these findings to any associated SREs. We hope that this pilot study will lead to larger studies with higher number of patients, longer follow-up periods, and will include patients with metastatic prostate cancer not receiving hormonal therapy as a comparative arm.

In conclusion, osteoporotic effect was demonstrated to start early after ADT, and early preventive measures should be considered in all the patients. The study showed no difference in effect on BMD between surgical castration and LHRH antagonists.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Faculty of Medicine, Alexandria University (April 2016).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

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Turk J Urol 2021; 47(2): 120-4
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