*Bratisl Lek Listy 2009; 110 (9)*
559 – 562

CLINICAL STUDY

# Evaluation of bone mass density on patients with prostate cancer prior to the start of androgen deprivation therapy

Ziaran S, Goncalves FM, Wendl J, Trebaticky B, Breza J Sn

*Department of Urology with Centre for Kidney Transplantation, Faculty of Medicine, Comenius University, Bratislava, Slovakia.* **stanoziaran@gmail.com**

**Abstract:** *Background:* Men with prostate cancer older than 60 years who are treated with androgen deprivation therapy (ADT) represent a specific subpopulation of patients being at high risk of bone loss and subsequent complications. In contrast to this fact, there is not much data (if any) about this specific subpopulation of men and their BMD prior to the start of ADT. The aim of this study is to evaluate BMD in such patients.
*Patients and methods:* Femoral neck and lumbar spine (L1–L4) were determined by dual-x-ray absorbtiometry (DXA) in 80 men (mean age 75.3 yrs, mean PSA 27.5 ng/ml) at the beginning of ADT.
*Results:* 38 out of 80 patients (47.5 %) had femoral and/or L1–L4 osteopenia, and 6 patients (7.5 %) were diagnosed with femoral and/or L1–L4 osteoporosis before the start of ADT. Less than a half (45 %) of examined patients had normal values of femoral and L1–L4 BMD.
*Conclusion:* Osteopenia is very common in men with prostate cancer who receive ADT. It is advisable to examine BMD prior to the start of ADT, and periodically thereafter. BMD measurement prior to ADT via DXA should be a common practice that can help in early detection of osteoporosis *(Tab. 3, Ref. 36).* Full Text (Free, PDF) *www.bmj.sk.*
Key words: osteopenia, osteoporosis in men, androgen deprivation therapy, prostate cancer.

A World Health Organization Working (WHO) Group has defined normal osteopenia, and osteoporosis in women based on bone mass density (BMD) compared with the value found in young adults (Tab. 1) (1). These WHO definitions are often applied to men. The fact whether the same limits should be used in men is controversial. Males have larger bones and a higher peak bone mass (2). Values between 1 and 2.5 SD below the young healthy mean are qualified as osteopenia, and values below 2.5 SD are identified as cases of osteoporosis. These cut-off levels were originally defined only for the measurements in women (3). When based on male cutoffs, 1–2 million (3–6 %) of men have osteoporosis and 8–13 million (28–47 %) have osteopenia; when based on female cutoffs, 280 000–1 million (1–4 %) have osteoporosis and 4–9 million (15–33 %) have osteopenia (4). While these numbers may seem disturbing, it is believed that osteoporosis in men is substantially underdiagnosed and undertreated in the United States and worldwide (5, 6).

Bone mineral density can be determined by means of several noninvasive methods (7). Dual-energy X-ray absorptiometry (DXA) is the method of choice for BMD measurement in most cases. This technique easily and precisely measures BMD at multiple skeletal sites with minimum radiation exposure (8, 9, 10). Measurements of biochemical markers of bone resorption, and bone formation in serum and urine complements the BMD assessment (11).

In men, osteoporosis occurs later than in women (12), but the prevalence of osteopenia does not differ significantly between men and women aged more than 50 years. Conversely, the prevalence of osteoporosis in men is lower than in women (4). Even though it may be underestimated when standard female BMD parameters are considered suitable for normal mineralization in men (13). BMD in men is generally higher than in women of the same age (14). Accordingly, the prevalence of male osteoporosis is greater when male-specific ranges are used in men over their fifties: ranging from 1 % to 4 % in elderly men when the diagnosis is based on female cut-off points vs 3 % to 6 % when based on male cut-off points (4). Unfortunately, no studies have been focused on finding the standard male BMD parameters that would be useful in evaluating the risk of fractures according to the degree of bone loss (2, 15).

**Tab. 1. WHO classification of osteoporosis.**

| Classification | Bone mineral density |
|---|---|
| Normal | -1.0 and above |
| Osteopenia | between -1.0 and -2.5 SD |
| Osteoporosis | -2.5 SD and below |
| Severe osteoporosis | -2.5 SD and below with fragility fractures |

SD – standard deviation

Department of Urology with Centre for Kidney Transplantation, Faculty of Medicine, Comenius University in Bratislava, Limbova 5, SK-833 05 Bratislava, Slovakia

**Address for correspondence:** S. Ziaran, MD, Dept of Urology, Faculty of Medicine, Limbova 5, SK-833 05 Bratislava, Slovakia.
Phone: +421.907835112
**Acknowledgement:** This research was supported by the UK Grant from the Comenius University in Bratislava No. UK/453/2009.

**Tab. 2. Evaluation of mean BMD and mean T-score of the cohort.**

| No of patients | BMD L1-L4 (g/cm$^2$) (mean) | T-score L1-L4 (mean) | BMD femur (g/cm$^2$) (mean) | T-score femur (mean) |
|---|---|---|---|---|
| 80 | 0.987 | -0.6 | 0.885 | -0.6 |

Similarly, prostate cancer affects men older than 50 years, and its prevalence increases with age. In Europe and United States, prostate cancer is the most commonly diagnosed malignancy in elderly men and the second leading cause of cancer-related deaths in the male population (16). It was more than 60 years ago, when Huggins and Hodges showed the relationship between prostate cancer and the effect of surgical and chemical castration (17). Since then, androgen deprivation therapy (ADT) is the mainstay treatment for advanced prostate cancer. However, the last decade saw a rise in concern about the adverse effect of ADT, especially bone loss (3, 17–22). This is due to the fact that BMD is directly related to bioavailable testosterone (23). Epidemiology data show that men with prostate cancer treated with ADT have a high prevalence of osteopenia and osteoporosis as determined by peripheral and central BMD measurements (24). Osteoporosis and osteopenia are common in the population affected by prostate carcinoma (21, 25). In contrast to this growing evidence, there is not much data (if any) about the specific subpopulation of men and their BMD prior to the start of ADT who are at high risk of BMD loss and consequent complications.

The aim of this study is to examine the initial BMD in men with advanced prostate cancer prior to the start of ADT, bring the initial measurement of BMD into physicians' attention, and put it into common practice.

## Materials and methods

We analyzed 80 consecutive patients (mean age 75.3 yrs, mean PSA 27.5 ng/ml) with locally advanced PCa. All patients had prostate biopsy. Femoral neck and lumbar spine were examined by DXA (Hologic) prior to the start of androgen deprivation therapy (ADT) between October 2006 and July 2008. Bone mass density of L1–L4, femoral neck, and T-score of L1–L4 and femoral neck were examined. All examinations were performed while using the same device and the results were assessed by the same osteologist.

All patients agreed to start ADT due to their pathologic stage or higher age. Patients with skeletal metastases diagnosed via skeletal scintigraphy were excluded from the study. All patients were examined with blood chemistry to exclude metabolic disorders, chronic renal failure, all were mobile, and patients had no history of pathologic fractures.

## Results

Altogether, 38 out of 80 patients (47.5 %) had femoral and/or L1–L4 osteopenia, and 6 patients (7.5 %) were diagnosed with femoral and/or L1–L4 osteoporosis before the start of ADT. Less than a half (45 %) of examined patients had normal values of femoral and L1–L4 BMD (Fig. 1). Mean BMD of L1–L4 of the cohort was 0.987 g/cm$^2$, median 0.985 g/cm$^2$ with mean T--score -0.6, median -0.6. Mean femoral BMD was 0.885 g/cm$^2$, median 0.885 g/ cm$^2$ with mean T-score -0.6, median -0.6 (Tab. 2). Femoral osteopenia was diagnosed in 17 patients, osteoporosis in 2. Osteopenia of L1–L4 was diagnosed in 11 patients, osteoporosis in 2. The diagnoses of both L1–L4 and femoral osteopenia were assessed in 10 patients, osteoporosis in 2 patients (Tab. 3).

## Discussion

Based on our findings, osteopenia is very common in prostate cancer patients prior to the start of ADT. Despite the lack of data concerning osteoporosis and osteopenia in patients prior to the start of ADT one study shows better results, namely 35.4 % had osteopenia with an increase up to more than 80 % after 10 years of ADT (18). No other particular data about BMD in men who are to undergo ADT were found using Medline/PubMed research facilities. In general, a large cross-sectional analysis showed that the vast majority of older men receiving ADT for prostate cancer have either osteopenia or osteoporosis (26).

BMD examination is necessary and should be advised. BMD is inversely correlated with fracture risk in men and women (27, 28). The risk of hip fracture related to age and BMD is similar in men and women (29). Available data confirm the frequent occurrence of vertebral fractures in men as well as in women (30, 31). Bone fractures often imply severe consequences for the quality of life. A proximal femur or vertebral fracture in an aged man is an event that often leads to permanent disability. The possibility of recovery from the event is minimal, with a 5-year mortality, which is significantly higher in men than in women (32). The mean prevalence of all bone deformities in women and men is similar, namely 12 % in females (range 6–21 %) and 12 % in males (range 8–20 %). These data show that the risk of skeletal events is similar in men and women in "normal" population.

Prostate cancer, orchidectomy and the use of ADT are associated with a markedly greater risk of fractures, especially those

**Tab. 3. Number of patients with osteoporosis or/and osteopenia.**

| Total patients=80 | Osteopenia (patients) | Osteoporosis (patients) |
|---|---|---|
| Femoral | 17 | 2 |
| L1–L4 | 11 | 2 |
| Femoral and L1–L4 | 10 | 2 |

of the hip (20). The one-year mortality rate in men after hip fracture is twice that in women (6). These alarming facts stress the importance of BMD examination in men with prostate cancer and their follow-up.

It is obvious that our cohort (80 men) is not big enough to state that osteopenia is a "pandemy", but it should draw physician's attention towards the patient's skeletal health before the initiation of ADT.

ADT for prostate cancer leads to significant bone loss (3, 17–22) and some studies show that the most significant bone mineral density loss occurs within the year 1 of androgen deprivation therapy (33). Moreover, ADT is associated with a four-fold increase in the incidence rate of both peripheral and vertebral fractures (34). Androgen deprivation therapy has other adverse effects on body composition including the decrease in lean body mass and muscle size (35). These body composition changes may result in frailty, and increase the risk of falls in older men (22). All these factors should be taken into consideration prior to the start of ADT. We fully agree that men treated with androgen deprivation therapy should have their BMD measured at the time of initiation of androgen deprivation therapy and periodically thereafter (36). This would help in early detection of osteoporosis (25) and enable early treatment. According to some authors, urologists should recommend a daily calcium intake (DCI) of >1000 mg in patients with prostate cancer, especially in those under ADT (19).

## Conclusion

Osteopenia is very common in men with prostate cancer who are to receive ADT. It is highly advisable to examine BMD prior to the start of ADT, and periodically thereafter. Periodic measurement of BMD after ADT would help in early detection of osteoporosis (25). Complications (fractures) resulting from osteoporosis are often severe (32) and this is why physicians (urologists) should always bear in mind the adverse effects of ADT and detect them early. BMD measurement prior to ADT via DXA should be a common practice.

## References

**1. Kanis JA, Melton LJ 3rd, Christiansen C, Johnston CC, Khaltaev N.** The diagnosis of osteoporosis. J Bone Miner Res 1994; 9: 1137—1141.

**2. Bilezikian JP.** Osteoporosis in men. J Clin Endocrinol Metab 1999; 84: 3431—3434.

**3. Kanis J, Melton III L, Christiansen C, Johnston C, Khaltaev N.** Perspective: the diagnosis of osteoporosis. J Bone Miner Res 1994; 9: 1137—1141.

**4. Looker AC, Orwoll ES, Johnston CC Jr, Lindsay RL, Wahner HW, Dunn WL et al.** Prevalence of low femoral bone density in older US adults from NHANES III. J Bone Miner Res 1997; 12: 1761—1768.

**5. Kiebzak GM, Beinart GA, Perser K, Ambrose CG, Siff SJ, Heggeness MH.** Undertreatment of osteoporosis in men with hip fracture. Arch Intern Med 2002; 162: 2217—2222.

**6. Kiebzak GM, Beinart GA, Perser K, Ambrose CG, Siff SJ, Heggeness MH.** Undertreatment of osteoporosis in men with hip fracture. Arch Intern Med 2002; 162: 2217—2222.

**7. Eastell R.** Treatment of postmenopausal osteoporosis. New Engl J Med 1998; 338: 736—746.

**8. Grampp S, Jergas M, Gluer CC, Lang P, Brastow P, Genant HK.** Radiologic diagnosis of osteoporosis. Current methods and perspectives. Radiol Clin North Am 1993; 31: 1133—1145.

**9. Bateman C.** South Africa under-prioritises osteoporosis. S Afr Med J 2006; 96: 19—20.

**10. Schousboe JT, Taylor BC, Fink HA, Kane RL, Cummings SR, Orwoll ES et al.** Cost-effectiveness of bone densitometry followed by treatment of osteoporosis in older men. J Amer Med Ass 2007; 298: 629—637.

**11. Smith MR.** Diagnosis and management of treatment-related osteoporosis in men with prostate carcinoma. Cancer 2003; 97: 789—795.

**12. Orwoll ES, Klein RF.** Osteoporosis in men. Endocrine Reviews 1995; 16: 87—116.

**13. Consensus Development Conference.** Diagnosis, prophylaxis, and treatment of osteoporosis. Amer J Med 1993; 94: 646—650.

**14. Seeman E.** Pathogenesis of bone fragility in women and men. Lancet 2002; 359: 1841—1850.

**15. Boonen S, Vanderschueren D.** Bone loss and osteoporotic fracture occurrence in aging men. 455—462. In: Lunenfeld B, Gooren L (Eds). Textbook of Men's Health. New York, Parthenon Publishing Group, 2002.

**16. Liska J, Repiska V, Galbavy S, Polak S, Varga I, Blasko M, Macejova D, Brtko J.** Prostate tumors histological classification and molecular aspects of prostate tumorigenesis. Endocrine Regulation 2007; 41: 45—57.

**17. Huggins C, Hodges CV.** Studies on prostatic cancer II: the effects of castration on advanced carcinoma of the prostate gland. Arch Surg 1941; 43: 209—223.

**18. Morote J, Morin JP, Orsola A, Abascal JM, Salvador C, Trilla E, Raventos CX, Cecchini L, Encabo G, Reventos J.** Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology 2007; 69 (3): 500—504.

**19. Planas J, Morote J, Orsola A, Salvador C, Trilla E, Cecchini L, Raventós CX.** The relationship between daily calcium intake and bone mineral density in men with prostate cancer BJU Int 2007;99 (4): 812—815.

**20. Abrahamsen B, Nielsen MF, Eskildsen P, Andersen JT, Walter S, Brixen K.** Fracture risk in Danish men with prostate cancer: a nationwide register study. BJU Int 2007; 100 (4): 749—754.

**21. Conde FA, Sarna L, Oka RK, Vredevoe DL, Rettig MB, Aronson WJ.** Age, body mass index, and serum prostate-specific antigen correlate with bone loss in men with prostate cancer not receiving androgen deprivation therapy. Urology 2004; 64 (2): 335—340.

**22. Fried LP, Tangen CM, Walston J et al.** Frailty in older adults: evidence for a phenotype. J Gerontol A Biol Sci Med Sci 2001; 56: M146—156.

**23. Scopacasa F, Horowitz M, Wishart JM, Morris HA, Chatterton BE, Need AG.** The relation between bone density, free androgen index, and estradiol in men 60 to 70 years old. Bone 2000; 27: 145—149.

**24. Bruder JM, Ma JZ, Basler JW, Welch MD.** Prevalence of osteopenia and osteoporosis by central and peripheral bone mineral density in men with prostate cancer during androgen-deprivation therapy. Urology 2006; 67 (1): 152—155.

**25. Agarwal MM, Khandelwal N, Mandal AK, Rana SV, Gupta V, Chandra Mohan V, Kishore GV.** Factors affecting bone mineral density in patients with prostate carcinoma before and after orchidectomy. Cancer 2005; 103 (10): 2042—2052.

**26. Malkowicz SB, Chu F, Forrest J, Smith MR, Price D, Sieber P, Barnette KG, Rodriguez D, Steiner MS.** ASCO Annual Meeting Proceedings Part I. J Clin Oncol 2007; 25 (8S): 5116.

**27. Cummings SR, Black DM, Nevitt MC et al.** Bone density at various sites for prediction of hip fractures. The Study of Osteoporotic Fractures Research Group. Lancet 1993; 341: 72—75.

**28. Seeley DG, Browner WS, Nevitt MC, Genant HK, Scott JC, Cummings SR.** Which fractures are associated with low appendicular bone mass in elderly women? The Study of Osteoporotic Fractures Research Group. Ann Intern Med 1991; 115: 837—842.

**29. De Laet CE, van Hout BA, Burger H, Hofman A, Pols HA.** Bone density and risk of hip fracture in men and women: cross sectional analysis. Brit Med J 1997; 315 (7102): 221—225.

**30. No authors listed.** Incidence of vertebral fracture in europe: results from the European Prospective Osteoporosis Study (EPOS). J Bone Miner Res 2002; 17 (4): 716—724.

**31. O'Neill TW, Felsenberg D, Varlow J, Cooper C, Kanis JA, Silman AJ.** The prevalence of vertebral deformity in european men and women: the European Vertebral Osteoporosis Study. J Bone Miner Res 1996; 11 (7): 1010—1018.

**32. Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA.** Mortality after all major types of osteoporotic fracture in men and women: an observational study. Lancet 1999; 353: 878—882.

**33. Israeli RS, Ryan CW, Jung LL.** Managing bone loss in men with locally advanced prostate cancer receiving androgen deprivation therapy. J Urol 2008; 179 (2): 414—423.

**34. López AM, Pena MA, Hernández R, Val F, Martín B, Riancho JA.** Fracture risk in patients with prostate cancer on androgen deprivation therapy Osteoporos Int 2005; 16 (6): 707—711.

**35. Smith MR, Finkelstein JS, McGovern FJ et al.** Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab 2002; 87: 599—603.

**36.Yaturu S, DjeDjos S, Alferos G, Deprisco C.** Bone mineral density changes on androgen deprivation therapy for prostate cancer and response to antiresorptive therapy. Prostate Cancer Prostatic Dis 2006; 9 (1): 35—38.

Received April 24, 2009.
Accepted May 28, 2009.