Relationship of Combined Androgen Deprivation Therapy and Bone Turnover Markers with Bone Mineral Density, Lean Body Mass and Fat Content in Patients with Non- Metastatic Prostate Cancer

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Abstract: Purpose: The purpose of this study is to determine the relationship between androgen deprivation therapy (Gonadotropin-releasing hormone agonists [GnRH agonist] and an androgen antagonist [Flutamide®] treatment) and markers of bone turnover and to measure bone mineral densities (BMD) and predictors of treatment-related changes in BMD and body composition in men with prostate cancer. **Methods:** Between January 2007 and March 2011, sixty seven consecutive men with prostate carcinoma aged 63 to 80 years (mean age 68.1 years) and 50 age-matched controls were included in this study. Men with prostate cancer were evaluated during initial and long-term GnRH agonist (Goserelin acetate) and an androgen antagonist (Flutamide®) treatment. The bone density in the third lumbar vertebra was measured using quantitative computed tomography (QCT). BMD of the proximal femur and total hip were measured by dual-energy x-ray absorptiometry. Parathyroid hormone (PTH), serum calcium, 25-hydroxyvitamin D and calcitonin were measured. Relationships between baseline characteristics (age, treatment duration, body mass index, and baseline values for outcome of interest) and changes in lean mass, fat mass, and BMD were assessed. **Results:** The mean age of cases was 68.1 years. Androgen deprivation therapy, resulted in decreased serum free testosterone concentrations to 2.2 pmol/L (normal range, 38 –114 pmol/L). Mean BMD of the postero-anterior lumbar spine decreased by 3.1% (P = 0.001), mean BMD of the total hip decreased by 4% (P = 0.02), mean BMD of the femoral neck decreased by 0.7% (P = 0.05), while mean BMD of the trochanter decreased by 1.4% in the androgen deprivation therapy group (P = 0.04). Patients who were treated for one year had less bone density than patients who were treated less than one year. Androgen deprivation therapy also decreased lean body mass by 2.0% (P= 0.007), increased fat mass by 6.6% at 12 months (P = 0.003), decreased the mean serum prostate specific antigen activities from 130.8 ng/mL to 4.4 ng/mL (P = 0.04). However, serum calcium, parathyroid hormone, and 25-hydroxyvitamin D measurements remained unchanged. The mean BMD levels were decreased significantly (all $p \leq 0.05$) in prostate carcinoma patients than in age-matched controls. **Conclusion:** In men with prostate cancer, androgen deprivation therapy increase bone turnover, decrease bone mineral density. So there is a need to measure bone mineral density and bone metabolic markers periodically and to evaluate secondary osteoporosis. Androgen deprivation therapy also increases fat mass, and decrease lean body mass.

[Hanan Shawky and Tarek Gamil. **Relationship of Combined Androgen Deprivation Therapy and Bone Turnover Markers with Bone Mineral Density, Lean Body Mass and Fat Content in Patients with Non-Metastatic Prostate Cancer** Journal of American Science 2012; 8(3): 384-390]. (ISSN: 1545-1003). http://www.americanscience.org. 51

Keywords: Prostate cancer**,** androgen deprivation therapy, gonadotropin-releasing hormone agonists, androgen antagonist, combined androgen blockade**,** osteoporosis, bone mineral density, bone turnover**.**

1. Introduction

Gonadotropin-releasing hormone agonists (GnRH agonist) and androgen antagonist are the mainstay of treatment for prostate cancer[1,2]. About one-third of the estimated two million prostate cancer survivors in the United States currently receive treatment with androgen deprivation therapy. Chronic administration of a GnRH agonist is the mainstay of treatment for metastatic prostate cancer. In addition, GnRH agonists are now a routine part of the management for many men with nonmetastatic prostate cancer[3,4]. Androgen deprivation therapy improve survival in men with locally advanced prostate cancer[5-8]. The benefits and harms of androgen deprivation therapy in other settings, including primary therapy for early stage prostate cancer and salvage therapy for rising levels of serum prostate specific antigen as the only indication of disease recurrence, have not been adequately defined[9]. The increased use of GnRH agonists has increased the importance of understanding and preventing treatment-related morbidity.

It was demonstrated that osteoporosis is an important complication of androgen deprivation therapy in men with prostate cancer. GnRH agonists increase bone turnover[10], decrease bone mineral density (BMD[10-13], and increase fracture risk[14-16] in men with prostate carcinoma. Androgen deprivation therapy also increase fat mass, decrease lean body mass[17,18] and decrease serum concentrations of

testosterone by over 95% and estrogen by approximately 80%[19,20].

These treatment-related changes in body composition may contribute to fatigue, vasomotor flushing, loss of libido, emotional distress, and decreased quality of life[9,21-23]. Whereas the consequences of initial GnRH agonist on BMD and body composition are well characterized, less is known regarding the long-term, treatment-related, adverse effects. In addition, little is known concerning the predictors of treatment-related changes in BMD and body composition.

We conducted this clinical study to evaluate the relationship between androgen deprivation therapy and treatment-related decreases in bone mineral density (BMD), changes in lean body mass, biochemical markers of bone turnover and fat mass in men with non-metastatic prostate cancer.

2. Materials and Methods

Patients and Study Design

Between January 2007 and March 2011, a series of 67 patients aged 63 to 80 years (mean age 68.1 years) with newly diagnosed, histologically confirmed non-metastatic adenocarcinoma of the prostate, and an elevated prostate specific antigen (PSA) level treated at Clinical Oncology Department, and Urology Department, Faculty of Medicine, Tanta University Hospital were eligible for this study. Data on 50 healthy age-matched controls were used for baseline biochemistry and densitometry assessment. These measurements were performed in these men for usage as comparative data.

Patients were evaluated at baseline and at 6, 12 and 36 months after commencing treatment with a long-acting GnRH agonist (Goserelin acetate, 3.6 mg subcutaneously monthly) and an androgen antagonist (Flutamide®, 750 mg daily). A serum sample was obtained at each visit and stored at -80°C.

No patient had thyroid, renal, or liver disease and none had received calcium, calcitriol, bisphosphonates, or calcitonin prior to entering the study. Eleven men had well controlled type II diabetes that was managed with oral hypoglycemic agents. Patients had a radionuclide bone scan within 6 months before study entry. Men with bone metastases or evidence of progressive disease were excluded. Men with metabolic bone disease, history of treatment for osteoporosis, history of deep venous thrombosis or pulmonary embolus, serum calcium less than 8.4 mg/dL or more than 10.6 mg/dL were also excluded. Other exclusion criteria included chronic use of glucocorticoids, or anticonvulsants, within 1 year. At a screening visit, BMD of the third lumbar vertebra was measured using quantitative computed tomography (QCT). Bone mineral densities of the proximal femur and total hip were measured by dual-energy x-ray absorptiometry.

All subjects continued treatment with androgen deprivation therapy throughout the study period. All subjects received calcium carbonate (500 mg daily) and a daily multivitamin containing vitamin D. All patients provided written informed consent prior to enrolment into the study. The Ethics Committee at our Faculty of Medicine, Tanta University granted protocol approval.

Study End Points

After informed consent was obtained venous blood and an early morning fasting 2-hours urine sample were collected from all men for biochemical and hormonal measurements. Serum and urinary calcium and creatinine levels and serum alkaline phosphatase activities were determined by routine auto Analyser methods. Serum parathyroid hormone, and serum 25 hydroxyvitamin D were measured by immunoradiometric assay. Serum free testosterone was measured by radioimmunoassay and serum prostate specific antigen by microparticle enzyme immunoassay.

Bone mineral densities of the third lumbar vertebra was measured using quantitative computed tomography (QCT), while, BMD of the proximal femur and total hip were measured by dual-energy x-ray absorptiometry. Bone mineral densities measurements were expressed in absolute terms as g/cm2 and as a percentage of the initial value.

Lean and fat mass also were determined by dual energy X-ray absorptiometry (software version 11.2) as described previously by Smith *et al.*[18]. Fasting subjects were weighed wearing a hospital gown and no shoes. Body weight was measured to the nearest 0.1 kg using a digital platform scale (Blue Bell BioMedical model 500; SR Instruments, Tonawanda, NY). Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer. The mean of three height measurements was recorded.

Statistical analyses

The primary outcomes were the percentage change in the BMD of the total hip, third lumbar vertebra, and proximal femur, as well as lean body mass, and fat mass from baseline to 36 months. Values are reported as means unless indicated otherwise. Changes were tested for significance using one-sample Student *t* tests. Univariate regression models were fit for changes in BMD, lean mass, and fat mass using each covariate as a single explanatory variable. Next, multivariate models were fit using all explanatory variables to identify those that were independently predictive. Percent changes in testosterone, and bone alkaline phosphatase were compared between groups using *t* tests. The covariates considered in the

regression analyses were age, duration of GnRH agonist treatment, body mass index (BMI), and baseline value for BMD, lean mass, or fat mass. All data were included in the efficacy analyses. All *P* values were 2 sided and *P*s ≤ 0.05 were considered to be statistically significant.

3. Results

Characteristics of the Patients

A series of 67 patients aged 63 to 80 years (mean age 68.1 years) with newly diagnosed, histologically confirmed adenocarcinoma of the prostate, and an elevated prostate specific antigen level treated at Clinical Oncology Department, and Urology Departments, Faculty of Medicine, Tanta University Hospital were eligible for this study.

All patients were receiving treatment with a long-acting GnRH agonist (Goserelin acetate, 3.6 mg subcutaneously monthly) and an androgen antagonist (Flutamide®, 750 mg daily). All patients continued androgen deprivation therapy throughout the study period. Data on 50 healthy age-matched controls were used for baseline biochemistry and densitometry assessment. These measurements were performed in these men for usage as comparative data. Baseline characteristics of men in both groups were comparable (Table 1), {All p = NS}.

Table (1): Baseline characteristics of men in both groups

Characteristics	Androgen deprivation therapy group **(67)**	**Control Group (50)**	***P* Value**
Age in years			
Mean	68.1	67.3	0.346
Median	67	66	
Range	63 - 80	61-78	
Body mass index, kg/m2	28.6	27.7	0.135
Testosterone, pmol/L			
Mean	38	43.7	0.093
range	38 – 112	40 – 114	
Mean Bone alkaline phosphatase, U/L	46	38	0.082
Total hip			
Mean bone mineral density, g/cm^2	1.01	0.98	0.453
Posteroanterior lumbar spine			
Mean Bone mineral density, g/cm2	1.07	1.08	0.166

Results of serum biochemistry, markers of bone turnover and bone densitometry performed at 0, 6, 12 and 36 months are recorded in Table 2.

Table (2): Serum biochemistry, markers of bone turnover, and bone mineral density measurements in men with prostate carcinoma at 0, 6, 12 and 36 months after therapy with combined androgen blockade and in healthy age-matched control

Characteristics	**Control group (50)**	Androgen deprivation therapy group **(67)**			
		Baseline (0 months)	**6 months**	**12 months**	**36 months**
Mean **calcium,** mmol/L	2.40	2.45	2.42	2.39	2.39
Mean **phosphate**, mmol/L	1.18	1.17	1.18	1.18	1.18
Mean **Creatinine**, mmol/L	0.11	0.11	0.10	0.11	0.10
Mean **parathyroid hormone,** pmol/L	3.8	3.6	3.5	3.4	3.3
Mean **free testosterone**, pmol/L	43.7	38	2.3	2.2	2.2
Serum gonadotrophin, mu/L	16	17	8	5	5
Mean **urinary calcium/creatinine ratio**, mmol/mmol	0.41	0.32	0.69	0.70	0.71
Mean **prostate specific antigen**, ng/mL	<4	130.8	6.8	4.4	4.3
Mean **bone alkaline phosphatase**, u/L	38	46	58	66	66
Mean **spinal bone** density measured by quantitative computed tomography, g/cm2	1.08	1.07	1.04	1.03	1.03
Mean **femoral neck** bone density measured by dual energy X-ray absorptiometry, g/cm2	0.94	0.94	0.93	0.93	0.93
Trochanter bone density measured by dual energy X-ray absorptiometry, g/cm2	0.89	0.88	0.87	0.86	0.86
Mean **total hip** bone density measured by dual energy X-ray absorptiometry, g/cm2	0.98	1.01	0.96	0.96	0.95

Combined androgen blockade resulted in achieving mean serum free testosterone concentrations of 2.2 pmol/L (normal range, 38–114 pmol/L) and serum gonadotrophin measurements of 5 mu/L (normal range, 5–21 mu/L). The mean serum prostate specific antigen activities decreased from 130.8 to 4.4 ng/mL (P = 0.04) after 12 months of therapy. Changes in serum bone specific alkaline phosphatase concentrations differed significantly between the groups. Serum bone-specific alkaline phosphatase increased by 25% in the androgen deprivation therapy group (P=0.003) from baseline to 6 months. The difference between the 2 groups in percent change from baseline to 12 months was 30% for bone-specific alkaline phosphatase.

Serum calcium, phosphate, and parathyroid hormone measurements remained unchanged during the study. No man had evidence of subclinical vitamin D deficiency.

Changes in BMD and Body Composition

At study entry, there was no evidence of bone metastases or osteosclerosis secondary to prostate carcinoma in any patient. Table 3 shows the percent change in BMD measurements in men treated with combined androgen blockade. Mean percent changes at 12 months in BMD and body composition differed significantly between the 2 groups (Table 3).

Table (3): Mean percent changes in BMD and Body Composition in both groups

Characteristics	% Change in androgen deprivation therapy group **(67)**	% Change in Control Group **(50)**	P Value
Trochanter			
Mean	-1.4	0	0.04
Femoral neck			
Mean	-0.7	0	0.05
Total hip			
Mean	-4	0.1	0.02
Posteroanterior lumbar spine			
Mean	-3.1	0.01	0.001
Fat mass			
Mean	6.6	0	0.003
Lean mass			
Mean	-2	0	0.007

Mean BMD of the postero-anterior lumbar spine decreased by 3.1% in the androgen deprivation therapy group (P = 0.001). Mean percent changes in BMD of the total hip, femoral neck and trochanter also differed significantly between the 2 groups (Table 3). Bone mineral density of the total hip decreased by 4% in the androgen deprivation therapy group (P = 0.02). Bone mineral density of the femoral neck decreased by 0.7% in the androgen deprivation therapy group (P = 0.05). Bone mineral density of the trochanter decreased by 1.4% in the androgen deprivation therapy group (P = 0.04). The differences between the 2 groups in percent change from baseline to 12 months were 3.09 for the postero-anterior lumbar spine, 3.9% for the total hip, 1.4% for the trochanter, and 0.7% for the femoral neck. Baseline BMD in the control group was not associated with significant changes in BMD. Duration of androgen deprivation therapy more than 1 year did not significantly predict changes in BMD in either univariate or multivariate analyses.

The mean lean body mass decreased by 2% (P = 0.007). The mean fat mass increased by 6.6% (P = 0.003). A higher fat mass at baseline was associated with less fat accumulation in both univariate and multivariate models. In contrast, baseline lean body mass was not associated with changes in lean body mass. In univariate models, a longer duration of androgen deprivation therapy was associated with less fat accumulation and less loss of lean body mass. Age was not associated with changes in fat mass, lean body mass, or BMD.

4. Discussion

Many studies have demonstrated that elderly men with advanced prostate carcinoma treated by either orchiectomy or with androgen blockade will experience hypogonadal symptoms and may be at risk for developing high turnover osteoporosis and skeletal fractures [1,13,24-30].

The key outcomes in these analyses were chosen to represent the bone, muscle, and fat compartments. The baseline characteristics of both groups were comparable in this study. In our study the mean lean body mass decreased by 2% (P = 0.007) and the mean fat mass increased by 6.6% (P = 0.003). In a 3-month study of 22 men with nonmetastatic prostate cancer, GnRH agonist treatment increased mean fat mass by 8.5% (P = 0.008) and decreased lean body mass by 2.6% (P = 0.003)[31]. Vermeulen et al[32] demonstrated that androgens are important determinants of body composition in men and serum testosterone concentrations correlate positively with muscle mass and negatively with fat mass[32]. In another 3-month prospective study of men with non-metastatic prostate

cancer, mean fat mass increased by 4.3% (P = 0.002) and lean body mass decreased by 1.4% (P = 0.006)[33]. Similarly, many investigators reported that GnRH agonist significantly decrease lean body mass and increase fat mass in men with prostate cancer[17,18,31,34,35]. The similarity of results between us and these studies suggests that body composition changes are an early adverse effect and may be clinically important even with short-term therapy.

We found that a longer duration of androgen deprivation therapy independently predicted less fat accumulation and less reduction in lean body mass during androgen deprivation therapy. Analyses of prospective changes in body composition during initial and long-term GnRH agonist treatment also suggests that fat mass increases and lean body mass decreases mainly during initial androgen deprivation therapy[36]. This was comparable to that reported by Smith *et al.*[37].

The histomorphometric changes of hypogonadism include high bone turnover[38], trabecular plate perforation, and osteoclast activation[39]. These findings often are reflected by increases in the noninvasive markers of bone turnover[40]. As demonstrated in this study, combined androgen blockade resulted in all men achieving castrate levels of serum free testosterone concentrations accompanied by significant increases in serum alkaline phosphatase activities. Similar findings have been noted by Percival *et al.*[27], who investigated 28 men with prostate carcinoma treated by orchiectomy. They found significant increases in serum alkaline phosphatase activities, associated with histologic evidence of active erosion surfaces.

Thus hypogonadism remains an important cause of male osteoporosis and skeletal fractures[38-42]. Both cortical and cancellous bone loss have been reported to occur within 6 months of developing hypogonadism after GnRH agonist therapy. Rates of bone loss vary depending on the methods of BMD assessment[13,43]. In this study, lumbar spine DXA measurements were confounded by coexisting spondyloarthropathy and hence spinal quantitative computed tomography, a more sensitive method of BMD analysis[44,45], was used to determine cancellous bone loss. In our study we recorded a 3.09% reduction in lumbar spine and a 0.7% reduction in femoral neck BMD after 12 months of therapy with a long-acting GnRH agonist (Goserelin acetate) and an androgen antagonist (Flutamide), in comparison with age-matched control group. The decrease in BMD was previously reported[10-12,34,46,47], and was much greater than expected in an age-matched control group[48]. Notably, high rates of bone loss were observed despite concurrent administration of supplemental calcium and vitamin D and careful exclusion of secondary causes of osteoporosis. This was comparable with that reported by Smith *et al.*[10,46].

In conclusion, our study demonstrated that, fat mass increases, lean body mass decreases and BMD decreases primarily during initial androgen deprivation therapy.

There are some potential limitations to this study. First, its small sample size with power limitations. Second, the study was powered to detect a significant change in BMD and was not powered to assess the impact on fracture risk. Finally, the patient population in this study was restricted to non-metastatic prostate cancer, and exclusion to men with bone metastases would not be appropriate.

Prospective studies with long-term follow-up are necessary to confirm the observed relations between duration of GnRH agonist treatment and subsequent changes in BMD and body composition. Additional larger studies also are needed to assess other covariates.

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5. References

1. Smith MR. (2007): Androgen deprivation therapy for prostate cancer: new concepts and concerns. Curr Opin Endocrinol Diabetes Obes.; 14 (3): 247–54.
2. Michaelson MD, Kaufman DS, Lee H, *et al.*(2007): Randomized Controlled Trial of Annual Zoledronic Acid to Prevent Gonadotropin-Releasing Hormone Agonist–Induced Bone Loss in Men With Prostate Cancer. J Clin Oncol.; 25 (9):1038-42.
3. Cooperberg MR, Grossfeld GD, Lubeck DP, *et al.* (2003): National practice patterns and time trends in androgen ablation for localized prostate cancer. J Natl Cancer Inst.; 95: 981–9.
4. Barry MJ, Delorenzo MA, Walker-Corkery ES, *et al.* (2006): The rising prevalence of androgen deprivation among older American men since the advent of prostate-specific antigen testing: a population-based cohort study. BJU Int.; 98: 973–8.
5. The Medical Research Council Prostate Cancer Working Party Investigators Group. Immediate versus deferred treatment for advanced prostatic cancer (1997): initial results of the Medical Research Council Trial. Br J Urol.; 79: 235–46.
6. Bolla M, Gonzalez D, Warde P, *et al.* (1997): Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med.; 337: 295–300.
7. Pilepich MV, Caplan R, Byhardt RW, *et al.* (1997): Phase III trial of androgen suppression

using goserelin in unfavorable-prognosis carcinoma of the prostate treated with definitive radiotherapy: report of Radiation Therapy Oncology Group Protocol 85–31. J Clin Oncol.; 15:1013–21.
8. Messing EM, Manola J, Sarosdy M, *et al.* (1999): Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med.; 341: 1781–8.
9. Sharifi N, Gulley JL, Dahut WL. (2005): Androgen deprivation therapy for prostate cancer. Jama; 294: 238–44.
10. Smith MR, McGovern FJ, Zietman AL, *et al.* (2001): Pamidronate to prevent bone loss during androgen deprivation therapy for prostate cancer. N Engl J Med.; 345: 948-55.
11. Maillefert JF, Sibilia J, Michel F, *et al.* (1999): Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol.; 161: 1219-22.
12. Diamond T, Campbell J, Bryant C, *et al.* (1998): 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: 1561-6.
13. Eriksson S, Eriksson A, Stege R, *et al.* (1995): Bone mineral density in patients with prostatic cancer treated with orchidectomy and with estrogens. Calcif Tissue Int.; 57: 97-9.
14. Shahinian VB, Kuo YF, Freeman JL, *et al.* (2005): Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med.; 352: 154-64.
15. Smith MR, Lee WC, Brandman J, *et al.* (2005): Gonadotropin-releasing hormone agonists and fracture risk: A claims-based cohort study of men with nonmetastatic prostate cancer. J Clin Oncol.; 23: 7897-903.
16. Smith MR, Boyce SP, Moyneur E, *et al.* (2006): Risk of clinical fractures after gonadotropin-releasing hormone agonist therapy for prostate cancer. J Urol.; 175:136-9.
17. Tayek JA, Heber D, Byerley LO, *et al.* (1990): Nutritional and metabolic effects of gonadotropin-releasing hormone agonist treatment for prostate cancer. Metabolism.; 39: 1314–19.
18. Smith MR, Finkelstein JS, McGovern FJ, *et al.* (2002): Changes in body composition during androgen deprivation therapy for prostate cancer. J Clin Endocrinol Metab.; 87: 599 – 603.
19. The Leuprolide Study Group. (1984): Leuprolide versus diethylstilbestrol for metastatic prostate cancer. N Engl J Med.; 311: 1281–6.
20. Garnick MB. (1986): Leuprolide versus diethylstilbestrol for previously untreated stage D2 prostate cancer. Results of a prospectively randomized trial. Urology; 27: 21–8.
21. Stone P, Hardy J, Huddart R, *et al.* (2000): Fatigue in patients with prostate cancer receiving hormone therapy. Eur J Cancer.; 36: 1134–41.
22. Potosky AL, Knopf K, Clegg LX, *et al.* (2001): Quality-of-life outcomes after primary androgen deprivation therapy: results from the Prostate Cancer Outcomes Study. J Clin Oncol.; 19: 3750–7.
23. Herr HW, O'Sullivan M (2000): Quality of life of asymptomatic men with nonmetastatic prostate cancer on androgen deprivation therapy. J Urol.; 163: 1743–6.
24. Clarke NW, McLure J, George NJR (1993): The effects of orchiectomy on skeletal metabolism in metastatic prostate cancer. Scand J Urol Nephrol.; 27: 475–83.
25. Mc Grath SA, Diamond T. (1995): Osteoporosis as a complication of orchiectomy in two elderly men with prostatic cancer. J Urol.; 154: 535–6.
26. Carlstrom K, Stege R, Henriksson P, *et al.* (1994): Effects of endocrine treatment on bone mineral markers in patients with prostatic cancer [abstract]. Scand J Urol Nephrol.; 161: 28–9.
27. Percival RC, Urwin GH, Harris S, *et al.* (1987) : Biochemical and histological evidence that carcinoma of the prostate is associated with increased bone resorption. Eur J Surg Oncol.; 13: 41– 6.
28. Daniell HW (1997): Osteoporosis after orchiectomy for prostate cancer. J Urol.; 157: 439–44.
29. Collinson MP, Tyrell CJ, Hutton C. (1994): Osteoporosis occurring in two patients receiving LHRH analogs for carcinoma of the prostate. Calcif Tissue Int.; 54: 327–8.
30. Maillefert JF, Sibilia J, Kuntz JL, *et al.* (1994): Gonadotrophin- releasing hormone agonists induce osteoporosis. Br J Rheumatol.; 33: 1199–200.
31. Smith JC, Bennett S, Evans LM, *et al.* (2001): The effects of induced hypogonadism on arterial stiffness, body composition, and metabolic parameters in males with prostate cancer. J Clin Endocrinol Metab.; 86: 4261–7.
32. Vermeulen A, Goemaere S, Kaufman JM (1999): Testosterone, body composition and aging. J Endocrinol Invest.; 22: 110–6.
33. Cook RJ, Coleman R, Brown J, *et al.* (2006): Markers of bone metabolism and survival in men with hormone-refractory metastatic prostate cancer. Clin Cancer Res.; 12: 3361–7.
34. Berruti A, Dogliotti L, Terrone C, *et al.* (2002): 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: 2361–7.
35. Smith M. (2004): Changes in fat and lean body mass during androgen deprivation therapy for prostate cancer. Urology; 63: 742–5.
36. Lee H, McGovern K, Finkelstein JS, *et al.* (2005): Changes in bone mineral density and body composition during initial and long-term gonadotropin releasing hormone agonist treatment for prostate carcinoma. Cancer; 104: 1633-7.
37. Smith MR, Fallon MA, Lee H, *et al.* (2004): Raloxifene to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial. J Clin Endocrinol Metab.; 89: 3841–6.
38. Jackson JA, Kleerekoper M, Parfitt AM, *et al.* (1987): Bone histomorphometry in hypogonadal and eugonadal men with spinal osteoporosis. J Clin Endocrinol Metab.; 65: 53– 8.
39. Manolagas SC, Jilka RL (1995): Bone marrow, cytokines and bone remodelling. N Engl J Med.; 332: 305–11.
40. Stepan JJ, Lachman M, Zverina J, *et al.* (1989): Castrated men exhibit bone loss: effect of calcitonin treatment on biochemical indices of bone remodeling. J Clin Endocrinol Metab.; 69: 523–7.
41. Jackson JA, Kleerekoper M. (1990): Osteoporosis in men: diagnosis, pathophysiology and prevention. Medicine; 69: 137–52.
42. Vermeulen A, Kaufman JM (1992): Role of the hypothalamo-pituitary function in the hypoandrodrogenism of healthy aging. J Clin Endocrinol Metab.; 75: 704–6.
43. Goldray D, Weisman Y, Jaccard N, *et al.* (1993): Decreased bone density in elderly men treated with the gonadotropin-releasing hormone agonist decapeptyl (D-Trp6-GnRH). J Clin Endocrinol Metab.; 76: 288 90.
44. Orwoll ES, Oviatt SK, Mann T (1990): The impact of osteophytic and vascular calcifications on vertebral mineral density measurements in men. J Clin Endocrinol Metab.; 70: 1202–7.
45. Reinbold WD, Genant HK, Reiser UJ, *et al.* (1986): Bone mineral content in early postmenopausal and postmenopausal osteoporotic women: comparison of measurement methods. Radiology; 160: 469–78.
46. Smith MR, Eastham J, Gleason D, *et al.* (2003): Randomized controlled trial of zoledronic acid to prevent bone loss in men undergoing androgen deprivation therapy for nonmetastatic prostate cancer. J Urol.; 169: 2008–12.
47. Daniell HW, Dunn SR, Ferguson DW, *et al.* (2000): Progressive osteoporosis during androgen deprivation therapy for prostate cancer. J Urol.; 163: 181–6.
48. Jones G, Nguyen T, Sambrook P, *et al.* (1994): Progressive loss of bone in the femoral neck in elderly people: longitudinal findings from the Dubbo osteoporosis epidemiology study. BMJ; 309: 691–5.

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