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Bone Mineral Density in Patients with Prostatic Cancer Treated with Orchidectomy and with Estrogens

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Abstract. Bone mineral density (BMD) and bone mineral content (BMC) were measured in the femoral neck area, trochanteric area and Wards triangle, and in the distal radius of the left forearm before and after 1 year of endocrine treatment in 27 patients with prostatic cancer. Eleven of the patients were treated with orchidectomy and 16 with combined oral and intramuscular estrogens. The patients were free from metastases during the entire observation period. In the orchidectomized patients, BMD and BMC of the distal radius decreased significantly following treatment, whereas no changes were observed in the estrogen-treated patients. These preliminary results demonstrate that estrogens may protect bone in male subjects also and may merit further investigations on larger groups of patients.

Key words: Bone mineral density — Bone mineral content — Prostatic cancer — Endocrine treatment.

Though the bone-saving effect of estrogen treatment in women is well known, few studies on the effects of different drugs on bone mass have been carried out in men. This also holds for the effects of castration as well as of the natural endocrine aging in healthy men. Furthermore, is not well known if bone tissue in men and women has a similar or different response to sex hormones. One obvious reason for this is the well-known unwanted effects following administration of hormones being more or less specific for the opposite sex. However, estrogen administration as well as orchidectomy are established modes of treatment of carcinoma of the prostate (CAP) and provide convenient models for the study of the effects of estrogens as well as of androgen deprivation on bone tissue in men. Clarke et al. [1] reported a decreased osteoid surface and an impaired bone mineralization in orchidectomized patients with CAP, and Goldray et al. [2] also reported decreasing bone mineral density (BMD) in men with benign prostatic hyperplasia treated by down-regulation of the testicular androgen synthesis by GnRH-analogs. However, as far as we know from the literature, nothing is known about the effects of estrogen on bone in men. The present paper describes the effects of estrogen treatment and orchidectomy on bone mass in men with CAP after 1 year of treatment.

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Materials and Methods

Subjects

Initially, 29 men with histologically confirmed CAP were recruited for the study. With the exception of their specific disease, all subjects were ambulatory, apparently healthy, medicine-free, and showed no clinical or laboratory signs of endocrine disorder, alcohol abuse or cardiovascular, renal, hepatic, biliary, or intestinal malfunction. Two patients were excluded from the study, one due to technical problems with the bone mass measurements and one patient interrupted the study.

The remaining study group comprised 27 men, aged 60–80 years. They were allocated to receive either orchidectomy (n = 11) or estrogen treatment (n = 16) irrespective of the classification of the tumor. Of the patients treated by orchidectomy, two were staged T0, two had T2, four had T3, and three had T4 tumors. The malignancy grade was G1 in one, G2 in five, and G3 in five patients. Of the patients treated with estrogens, one was staged T0, four had T2, six had T3 and five had T4 tumors. The malignancy grade was G1 in one, G2 in ten, and G3 in five patients. Bone scintimetry was performed in all patients, and the patients included in the study were free from metastases before as well as after 1 year of treatment.

Bilateral orchidectomy was performed under general anesthesia. Estrogen treatment included polyestradiol phosphate (Estradurin®, Pharmacia Therapeutics AB, Hälsingborg, Sweden) given intramuscularly at a dose of 160 mg every fourth week during the first 3 months and subsequently at a dose of 80 mg every fourth week in all 16 patients. Ethinyl estradiol (Etivex®, Pharmacia Therapeutics AB) was given orally at a dose of 2 × 0.5 mg daily during the first 2 weeks and after that at a dose of 0.15 mg daily in nine of the patients. In seven patients, oral estrogens were not given until after 3 months of single drug intramuscular estrogen treatment. Venous blood samples for analysis of pretreatment serum hormone concentrations were collected between 0900 and 1200 1–4 weeks before the start of the treatment.

The study was approved by the Ethical Committee, Huddinge University Hospital and informed consent was obtained from all patients participating in the study.

BMD Measurement

The techniques for BMD measurements have been described in detail in a previous study [3]. Before and after 1 year of treatment, bone mineral measurements on the left proximal femur were performed using dual-photon densitometry (Lunar Radiation Co, Madison, WI) with a ^{153}Gd radiation source. The femoral neck, trochanteric, and Wards triangle areas were investigated and the results were expressed in g/cm^2. The bone mineral of the left forearm distal radius was analyzed with single photon densitometry (Lunar Radiation Co) with a ^{125}I radiation source. Five scans were examined just proximal to the bifurcation of the radius and ulna. The results were

Table 1. BMD (g/cm^2) and BMC (g) before and after 1 year of treatment and pretreatment serum concentrations of testosterone (T), SHBG, DHAS, and cortisol in patients with prostatic cancer treated with orchidectomy and with estrogens, respectively

	Orchidectomy (n = 11)		Estrogens (n = 16)	
	Before	After	Before	After
Age years	73.9 ± 1.5		71.4 ± 1.3	
BMD femoral neck	0.83 ± 0.05	0.75 ± 0.06	0.83 ± 0.03	0.82 ± 0.04
BMD Wards Δ	0.75 ± 0.06	0.62 ± 0.06	0.67 ± 0.03	0.65 ± 0.05
BMD trochant.	0.76 ± 0.04	0.64 ± 0.07	0.79 ± 0.03	0.77 ± 0.04
BMC distal radius	1.14 ± 0.06	1.08 ± 0.06[b]	1.07 ± 0.06	1.04 ± 0.07
BMD distal radius	0.44 ± 0.02	0.42 ± 0.02[a]	0.39 ± 0.02	0.39 ± 0.02
T, nmol/liter	21.3 ± 2.3		23.3 ± 3.4	
SHBG, nmol/liter	43.3 ± 6.4		44.2 ± 5.9	
DHAS, nmol/liter	1609 (934–4409)		1860 (747–5977)	
Cortisol, nmol/liter	374 ± 35		371 ± 39	

Mean and SEM median and range with orchidectomy and estrogens, respectively
Significance of difference between pretreatment and treatment values is indicated by [a]$P < 0.05$ and [b]$P < 0.01$

expressed in g and g/cm, respectively. The short-term precision of the method was 2.2% in the radius, 2.7% in the trochanteric area, and 2.9% in the femoral neck and Wards triangle. The accuracy was 3% in the radius and 3–4% in the other areas.

Assay Methods

Pretreatment serum concentrations of testosterone, sex hormone binding globulin (SHBG), cortisol, and dehydroepiandrosterone sulfate (DHAS) were determined by radioimmunological or (SHBG) immunoradioimetric methods, for which details have been given previously [4].

Statistical Methods

Statistical analysis was performed by *t*-test for paired or unpaired observations and by Mann-Whitney U-test according to distribution.

Results

When the patients were compared with an age-matched healthy reference population, normal pretreatment endocrine data were found in all subjects. There were no differences in pretreatment endocrine data between the patients treated with estrogens and those treated by orchidectomy (Table 1). Scintimetry after 1 year showed no signs of metastases in any of the patients. The patients tolerated the treatment except for one orchidectomized patient who complained of extreme perspiration during treatment.

The results from bone mineral measurements showed a significant decrease in BMD as well as bone mineral content (BMC) in the distal radius in patients treated with orchidectomy (Table 1). A similar tendency was also noted for the BMD in the proximal femur, although the difference did not reach statistical significance. No changes in BMD were noted in the group treated with estrogens.

Discussion

Castration values for serum testosterone are achieved within 2 weeks with this form of estrogen treatment [5]. Furthermore, the oral estrogen component causes a tremendous increase in serum SHBG and in fact, circulating concentrations of biologically active testosterone are even lower than in orchidectomized subjects [4]. On the other hand, circulating concentrations of the major adrenal androgen DHAS and other adrenal androgens are almost unaffected by this estrogen treatment as well as by orchidectomy [6]. Strong associations between DHAS and also the free steroid DHA and bone mineral status have been found in postmenopausal women [7, 8], perhaps reflecting the unique character of DHAS, and especially DHA, of being weak androgens as well as compounds with direct estrogenic properties [9]. However, the almost identical DHAS levels in the two groups make differences in adrenal androgen status less possible as a reason for the differences in bone mass found during treatment.

In the orchidectomized patients, BMD decreased in all areas studied, but the changes reached statistical significance only in the distal radius. This difference in statistical significance may be explained by the lower degree of precision and accuracy of the measuring technique in the areas other than the radius and also by the limited number of observations. Further studies on larger populations may therefore be justified. Our finding of decreased BMD as well as BMC in the distal radius in the orchidectomized patients within 1 year of treatment confirms previous findings of bone loss in patients with prostatic disease treated by surgical castration or by down-regulation by GnRH analogs [1, 2]. The positive effects of estrogens as well as androgens upon

bone are well known. Besides his testosterone, the intact adult man also has considerable amounts of circulating estrogens, comparable to the lower range of those found in the early follicular phase in menstruating women [10]. Surgical castration as well as GnRH analog treatment result in a barren endocrine environment, almost completely devoid of any biologically active testosterone and with only 50% left of the estrogens [6, 11]. In fact, being in this situation a man is even more deprived of circulating sex steroids than a postmenopausal woman, as in the latter, the ovary still produces substantial amounts of testosterone [12]. The bone loss following orchidectomy or GnRH analog treatment is therefore not surprising.

Unchanged BMD and BMC values were found in the estrogen-treated patients, clearly indicating that this form of estrogen has a protective effect on bone in men. Oral estrogen treatment of CAP is associated with severe cardiovascular side effects [13]. Therefore we have now substituted this treatment regimen by single drug parenteral treatment with polyestradiol phosphate, by which castration levels of testosterone are reached within 1 month [14]. This latter form of estrogen treatment seems to be free from cardiovascular side effects and its therapeutic efficacy is comparable to orchidectomy [15–17]. In a recent preliminary study [18], we have found that this form of estrogen treatment results in unchanged serum levels of biochemical markers of bone loss (osteocalcin, procollagen III P), whereas orchidectomy resulted in increased serum concentrations, indicating bone loss. Therefore estrogen treatment in general seems to have a protective effect on bone in patients with CAP.

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