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Estrogens and euosteogenesis in men

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Abstract. – **The bone mineral density (BMD) has been analyzed in 200 male patients divided in 4 groups of age as follows: (A) 40-49, (B) 50-59, (C) 60-69, and (D) 70 years and above. BMD was measured by using the DEXA technique both in the ultradistal and mediodistal region of radius of the non-dominant side. In addition, the serum levels of testosterone (Ts), dihydrotestosterone (DHT) and 17-β estradiol (E-2) have also been measured.**

The data obtained have shown that bone mineral density values are decreasing also in the males with advancing age, and the positive correlation ($p< 0.05$) of BMD with the E-2 levels also tend to decrease.

These results suggest the hypothesis that the true sexual hormones regulating the rhythm of osteogenesis may be the estrogens in the males, too.

Key Words:

Osteporosis, Bone mineral density, Testosterone, Dihydrotestosterone, 17-β estradiol (E-2).

Introduction

The chronology of andropausal events cannot be detected with certainly in men, although it is taking place around the 6th and 7th decades of the life. Androgens certainly have an impact on the osteogenesis, because there are some androgen receptors on the bone cells, and androgen deficiency may have some effects on the bone turnover, both directly and indirectly. Apart from the pathogenetic processes deriving from aging of the bone, one can attribute also a role to the decreasing androgenic effects. For example, Vermeelen et al[1] have observed a decrease of the plasma testosterone levels from the 6th decade of life, with wide individual variations. Others have described a decrease of the binding sites (androgen binding protein = ABP) between the 7th and the 8th decade of life[2]. These latter results suggest either a decreased synthesis, or an increased degradation of ABP in the older men, together with a decreased androgen availability manifesting itself in a lower rate of spermatogenesis, and at the same time, in the available estrogens, like FSH.

Other authors have observed a decrease of the free testosterone and a parallel increase of the sex hormone binding globulin (SHBG), being accompanied by a considerable decrease of the dihydrotestosterone (DHT) around the age of 60 years[3]. The increased SHBG production causes a decreased clearance of testosterone and DHT, as well as of their free fractions being responsible for the hormonal actions. On the other hand, the increased levels of SHBG after the 6th decade reflects most probably the increase of estrogens observed by various authors in aging men, attributed to an enhanced peripheric aromatization of the androgens, because the estrogens have a marked stimulation of the SHBG production[4].

The correlation between bone mineral density and serum testosterone concentrations has been demostrated only by a few studies, i.e., the causal role of male hypogonadism in osteoporosis is by far not so evident than in females. The pathogenetic components of the basis of male osteoporosis are considered to be multiple central neurogenic, pituitary and testicular, as well as of peripheric character[5]. The positive effects of testosterone on tissues of the skeleton are not realized only through the anabolic influences, but a direct effect has also been documented. As a matter of fact, the presence of specific testosterone receptors has been described on the osteoblasts[6], the consequence of which

may be that testosterone treatment stimulates both the replication and the functional capacity of the osteoblast, as shown by an increased osteocalcine production and a dcreased hydroxyprolinuria[7]. It is not excluded that such a positive effect is also supported by the activation of dihydroxy-vitamin D[8].

In any case, the elderly subjects should be considered in their globality, in which physiological and pathological events are expressed involving various organs and apparatures. These events may start from the neurotransmitter fluctuations and can arrive to the compromised functions of receptors for gonadotropic or androgenic hormones. In this global view of the elderly, eventual alterations of the hormone secretions may become of higher responsability. Therefore, the present study was aimed at revealing, whether the senile osteoporosis of men has different pathogenetic aspects compared to that of the females, as well as at evaluating the significance of andropause in the formation of this disease.

Materials and Methods

Our study was performed on 200 male patients divided in 4 groups of age as follows: (A) 40-49, (B) 50-59, (C) 60-69 and (D) 70 years and above. The bone mineral density (BMD) has been measured by DEXA technique in all patients both in the ultradistal (UDBMD) and mediodistal (MDBMD) region of radious on the non-dominant side, by means of an X-ray mineralometer Lunar DPX.

Serum testosterone (Ts) and 17-b estradiol (E-2) levels were measured with radioimmunoassay (RIA) using the Immunocoat-I-125-Testosterone, and Immunocoat-I-estradiol Kits, respectively, both of them are products of Pantex (Santa Monica, Ca, USA). Serum dihydrotestosterone (DHT) was measured also by RIA technique applying the proper kit of Diagnostic Biochem, Canada Inc.

Statistical evaluation of the results obtained was performed by means of linear correlation analysis of Pearson.

Results

Tables I and II summarize the average results obtained in group A-D. The BMD values tend to decrease with advancing age, however, neither of the observed differences are significant between the adjacent age groups. Nevertheless, both UDBMD and MDBMD display an age-dependent declining tendency. Namely, the mean values of these parameters in group D differ significantly from those of group A and B in statistical terms, however, do not, when compared to group C.

The hormone levels Ts, DHT and E-“ also display an age-dependent decline in Groups A-D (Table I). These declines are statistically significant. We have also calculated the ratio DHT/Ts (Table I) which seems to increase with advancing age.

When analyzing the internal correlations of various parameters (Table II), none of the BMD values display any significant correlations with Ts, DHT or E-2 levels, except the

Table I. Description of the data obtained in the 4 age groups (mean ± SD)·

Parameters	Group A	Group B	Group C	Group D
Number of patients	50	50	50	50
Mean age (years)	45 ± 4	56 ± 3	65 ± 5	76 ± 5
Age range	41 – 49	50 – 59	60 – 69	70 – 81
UDBMD (mg/cm^2)	480 ± 80	476 ± 84	460 ± 80	430 ± 78
MDBMD (mg/cm^2)	765 ± 110	760 ± 112	730 ± 106	688 ± 102
Ts (ng/ml)	7.5 ± 3.6	7.0 ± 3.2	6.5 ± 2.9	5.6 ± 3.2
DHT (ng/ml)	0.82 ± 0.22	0.78 ± 0.20	0.75 ± 0.18	0.70 ± 0.20
E-2 (pg/ml)	58 ± 25	56 ± 22	56 ± 28	46 ± 20
DHT/Ts	0.109	0.111	0.115	0.125

Table II. Internal correlation of variuous parameters and their significance levels.

Parameters	Group A		Group B		Group C		Group D	
	r	p	r	p	r	p	r	p
UDBMD/Ts	0.108	NS	0.126	NS	0.246	NS	0.176	NS
UDBMD/DHT	0.112	NS	0.136	NS	0.212	NS	0.208	NS
UDBMD/E-2	0.186	NS	0.212	NS	0.306	NS	0.472	0.05
MDBMD/Ts	0.214	NS	0.184	NS	0.236	NS	0.484	NS
MDBMD/DHT	0.122	NS	0.212	NS	0.224	NS	0.464	NS
MDBMD/E-2	0.226	NS	0.286	NS	0.380	NS	0.482	0.05

Notes: r = correlation coefficient; p = significance; NS = not significant.

Group D, where both UDBMD and MDBMD correlate positively with E-2 at a statistically significant level.

Discussion

Nowadays there is a general consensus on the age-dependent decline of the production of sexual steroids (androgens and estrogen) both in males and females. It should be noted, however, that although the male gonads display a slow and progressive functional loss during aging, which results in a decrease of testosterone levels, one can find always some testosterone values even up to the age of 90 years, falling in the ranges of the young-adult individuals. If one is interested only in the interrelationships between the sexual hormones and the osteogenesis, it may seem to be logical to assume that similary as in the females, where the menopausal decline of estrogens is accompanied by a loss of bone minerals, the androgen deficiency occurring typically in the andropause of men should be accompained by a bone mineral loss.

As a matter of fact, the bone cells have receptors for both the estrogens and the androgens, therefore, the question arises, why the estrogen deficiency causes rapidly osteoporosis in the women, whereas in men the androgen deficiency is hardly causing similar events.

It has recently been demonstrated in rats that both the estrogens and the androgens have similar inhibitory effects on the gene expression of interleukin-6 (Il-6), which is known as a cytokine causing osteopenia. If Il-6 is not properly inhibited by either estrogens or androgens, it causes an up-regulation of the osteoclastogenesis[9].

On the other hand, a loss of bone minerals was observed in male, castrated rats[10], and this process was successfully recuperated by estrogen, but not by androgen treatment. The eventual role of estrogens in males has been shown in studies on the hypogonadial osteoporosis which is associated by low estrogen levels[8].

In case of receptor mutation resulting in an estrogen insensibility of a young man, Smith et al.[16] described very low BMD levels, normal Ts values, and very high estrogen levels. The only explanation for these findings may be that the true osteoregulatory sexual hormones are, strictly speaking, the estrogens also in men; they may act directly and specifically on the bone cells. This assumption involves that an adequate supply of estrogens would be necessary also in men for the maintenance of proeuosteogenetic tone, meanwhile the androgens may act only indirectly, either as precursors of estrogens (a process of local aromatization may transform the androgens in estrogens), or as anabolic agents increasing the muscle mass representig some valid physicomechanical stimuli for the euosteogenesis in the bones of the locomotive system.

On the basis of our observation and the available data of others, we assume that a regular osteogenesis always requires adequate sexual hormone levels, especially of the estrogens also in men.

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