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ORIGINAL ARTICLE

Testosterone levels and bone mineral density in young healthy men and in young infertile patients

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Abstract

OBJECTIVES. Although relatively little information exists concerning bone mineral density (BMD) in men, it has been demonstrated that similarly to observations in women, BMD decreases also with age in men, although to a smaller extent, and osteoporosis is increasingly recognized. Most reports concentrate, however, on men of advanced age. Therefore, we decided to investigate BMD in young healthy volunteers and in young patients suffering from infertility, and to compare it with serum testosterone levels.

MATERIAL AND METHODS. The study was performed on 80 men divided into two groups. The first group consisted of 39 young healthy men (mean age 22.1±0.3 years; range 20–29). The second group consisted of 41 infertile men with oligozoospermia (mean age 28.0±0.5 years; range 23–34). Serum testosterone levels and BMD were measured in each subject.

RESULTS. Decrease in BMD (T-score below –0.3) was observed in 35.9% of the subjects in the group of young healthy men and in 60.9% of the subjects in the group of infertile patients. Among these numbers osteopenia (T-score between –1 and –2.5) was found in 4 subjects (10.3%) in the group of young healthy men and in 13 subjects (31.7%) in the group of infertile patients. There was a positive correlation between testosterone concentrations and BMD as well as T-score both in healthy subjects and in infertile patients.

CONCLUSION. Results of the present study indicate that attention should be paid to testosterone deficiency in the young age in terms of the potential risk of decreased bone mineral density in the advanced age.

Introduction

There are extensive data on post-menopausal osteoporosis in women. Relatively little information exists concerning decreased bone mineral density (BMD) in men. However, it has been demonstrated that similarly to observations in women, BMD decreases also with age in men, although to a smaller extent [1–3], and osteoporosis is increasingly recognized.

Although osteoporosis in men is multifactorial [4] the important factor causing a decrease in BMD, leading to osteopenia or osteoporosis, is suggested to be a decrease in testosterone levels in aging [5–8]. Most reports concentrate, however, on men of advanced age. It has been shown that hypogonadal old men have low bone mass, and that testosterone replacement therapy may have positive effects on bone density in these subjects [9]. Testosterone treatment was also beneficial for eugonadal men with osteoporosis [10]. Moreover, low BMD was shown in young males with delayed puberty and idiopathic hypogonado-tropic hypogonadism, but only the former responded to one-year testosterone therapy [11].

We have shown recently that in subjects treated at a health resort, in screening examinations of heel bone, osteopenia has been found in 45%, and osteoporosis in 28.4% of 1494 men aged 50-59 years [12] but in examinations of anterioposteral lumbar spine (L2-L4) of 1,811 men aged over 60 years osteopenia has been found in 30.7%, and osteoporosis in 8.7% [13]. Therefore, we decided to investigate BMD in young patients suffering from infertility and in young healthy volunteers, and to compare it with serum testosterone levels.

Material and Methods

The study was performed on 80 men. The subjects were divided into two groups. The first group consisted of 39 young healthy men aged 22.1±0.3 years (mean±SEM; range 20-29). The second group consisted of 41 infertile men with oligozoospermia, aged 28.0±0.5 years (mean±SEM; range 23–34). Serum testosterone levels and bone mineral density were measured in each subject. Blood samples for testosterone estimation were collected at 08:00h and allowed to clot for 45 min; serum was removed after centrifugation and stored at -20ºC until assayed. Testosterone concentration was measured using RIA kits (Orion Diagnostica, Espoo, Finland); intra-assay CV – 3.8-7.5%, inter-assay CV – 4.8-7.0%, sensitivity – 0.03 ng/ml. BMD was measured at anterioposterior L2-L4 using dual-energy X-ray absorptiometry with Lunar DPX-L analyzer. Daily calibration and quality control were done regularly according to manufacturer's recommendations. The *in vitro* precision using the spine phantom provided by manufacturer was 1%. *In vivo* coefficient of variations was 3%. The data were statistically analyzed using Student's T-test and regression coefficient analyses.

The study has been approved by the Regional Ethical Committee. The experimental protocol was explained to each subject, and informed consent was obtained.

Results

Decrease in BMD was observed in many subjects in both groups of young men. Slightly decreased BMD (T-score between –0.3 and –1) was observed in 10 subjects (25.6%) in the group of young healthy men, and in 11 subjects (26.8%) in the group of infertile patients. Osteopenia (T-score between –1 and –2.5) was found in 4 subjects (10.3%) in the group of young healthy subjects and in 14 subjects (34.1%) in the group of infertile patients. The mean values of testosterone, BMD and T-score in both examined groups are shown in Fig.1. Testosterone levels, BMD and T-score in infertile patients were significantly lower than in healthy subjects. There is a positive correlation between testosterone concentrations and BMD as well as T-score both in healthy subjects and in infertile patients (Fig. 2).

Discussion

Results of our studies indicate that decrease in BMD occurs not only in men of advanced age but also in young healthy subjects, and is rather common in the group of young infertile patients with low testosterone levels. Moreover, correlation between BMD and testosterone concentrations exists in both groups.

For many years osteoporosis was generally regarded as a disease of women, related to the decline in estrogen levels that occurs at the menopause and predisposes to osteoporotic fractures (especially hip fractures) in advanced age [14-16]. In 1990, about 1.7 million hip fractures occurred worldwide. However, as many as 30% of this total number of hip fractures occurred in men [17]. Moreover, it is predicted that by the year 2025 the total number of hip fractures will reach almost 4 million (including 1.2 million of fractures in men), and this figure is projected to rise to 6.3 million by 2050 [17]. The results of a population-based, cross sectional study in the Czech Republic documented osteoporosis in 53% of women and in 56% of men over 75 [18]. Therefore, osteoporosis in men will become an increasing worldwide health problem over the next 25 years [7, 8, 19], especially

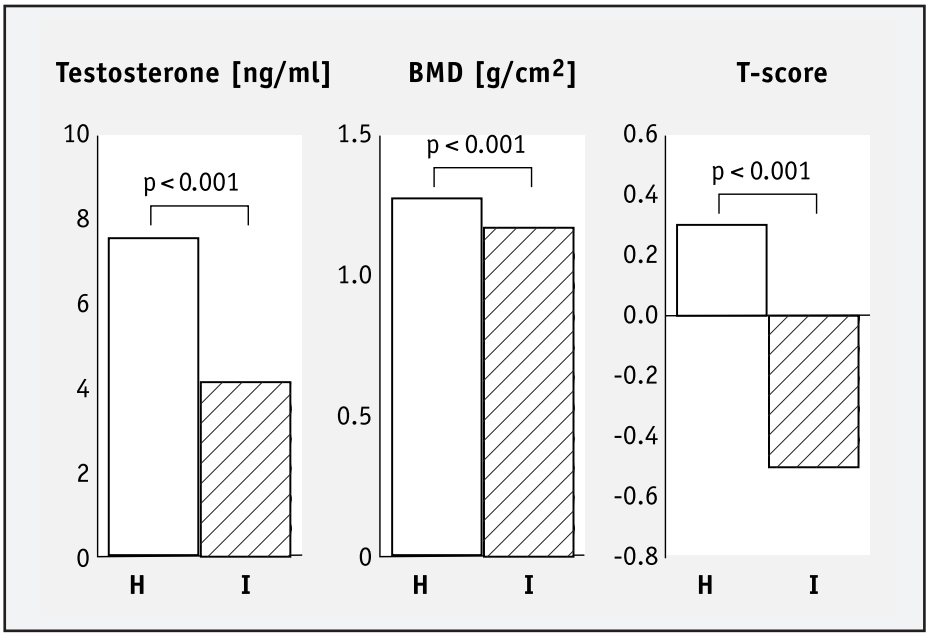

Fig. 1. Testosterone concentration, bone mineral density (BMD) and T-score in young healthy men (H) and in young infertile patients (I).

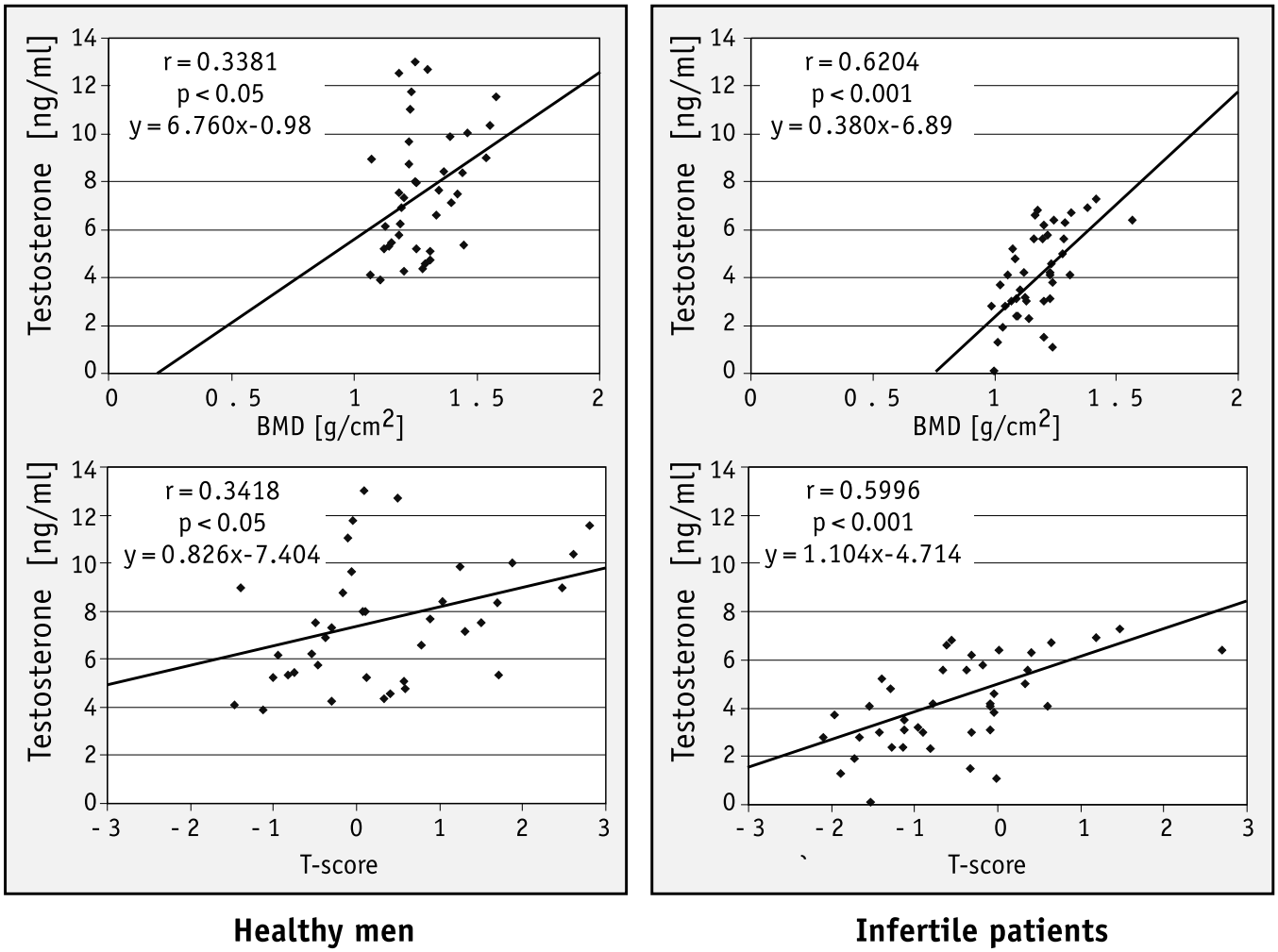

Fig. 2. Correlation between testosterone concentration and bone mineral density and T-score in young healthy men and in young infertile patients.

because the morbidity and mortality of hip fractures is higher in men than in women [19, 20].

The peak bone mass occurs in men slightly later than in women, corresponding to the later onset of puberty [21] and its determinants in men include race, genetic factors, hormonal factors, diet and exercise [19]. According to Cassidy [22] osteopenia and osteoporosis have their origins in childhood and adolescence. An important determinant of future fracture risk and osteoporosis is the peak bone mass achieved during the second decade of life. If the hereditary determined peak bone mass is not established during that time, the patient will enter young adulthood with osteopenia, and accelerated age-related osteoporosis.

Bone loss with aging may reach 5-10%/decade, and overall loss of peak bone mass from 20 years to advanced age may reach 5-15% for cortical bone and 15-45% for trabecular bone, and may be result of low calcium intake and absorption, low testosterone levels, increased parathyroid hormone levels, declining renal function, vitamin A deficiency and low physical activity [19, 23–25]. In addition to the bone loss associated with aging there are several factors associated with secondary osteoporosis, including hypogonadism, corticosteroid therapy, high alcohol consumption, smoking, transplantation, and also gastrointestinal disorders, hyperparathyroidism, hypercalciuria, hyperthyroidism and immobilization [7, 8, 19].

It has been shown that in the group of 28 patients between 21 and 49 years of age (mean age – 42.8 years) with a fracture or T-score below –2.5 SD, 17 patients (60.7%; mean age – 41.7 years) had secondary osteoporosis due to hypogonadism (35.3%), alcoholism, mastocytosis, primary biliary cirrhosis, osteogenesis imperfecta, idiopathic hypercalciuria, corticosteroid treatment, ankylosing spondylitis or multiple causes, but as many as 11 patients (39.3%; mean age – 44.6 years) had primary or idiopathic osteoporosis [26].

Primary or secondary hypogonadism has been recognized as one of the major causes of osteoporosis in men. Hypogonadal osteoporosis is associated with increased bone resorption and decreased mineralization, which can be reversed by treatment with testosterone [27]. On the basis of a highly significant association found between hypogonadism and minimal trauma hip fracture, a conclusion has been drawn that hypogonadal elderly men may be at increased risk for minimal trauma hip fracture [28].

On the other hand, there are relatively few studies, which examine the relation between BMD and gonadal steroids in men. Serum free testosterone, but not total testosterone concentrations, was significantly correlated to BMD in healthy volunteers aged 20-79 years [29]. On the other hand, an inverse correlation between total testosterone and BMD at the femur and whole body was found in men over age 75, whereas no such correlation was observed between BMD and free testosterone [8]. Lower BMD was found in hypogonadal males by many authors [30–35]. Decreased free androgen index was found in 12 men aged 27-55 years with idiopathic osteoporosis in comparison with 12 age-matched healthy men. Interestingly, a low free androgen index was accompanied by decreased estradiol levels and elevated sex hormone-binding globulin [36]. Decreased testosterone concentrations were observed in males (mean age – 73 years) with hip fractures in comparison with age-matched community-living men [37]. However, no changes in serum testosterone levels were found in men with primary osteoporosis and vertebral fractures [38]. Moreover, no correlation has been found between testosterone levels and BMD in 242 men aged 50-80 years [39]. On the basis of a weak correlation observed between sex hormones and markers of bone turnover in young men (20-40 years old), and lack of such correlation in older men Fatayerji and Eastell [40] suggest that sex hormones are more important for attainment of peak bone mass than bone loss in the elderly.

Although there is no well-established treatment for idiopathic osteoporosis in men, testosterone supplementation in hypogonadal osteoporosis resulted in an increase in BMD [9–11, 32, 41, 42]. Testosterone treatment in hypogonadal men corrects calcium malabsorption and increases 1,25-dihydroxyvitamin D levels, leading to an improvement in calcium balance and an increase in bone formation [43]. Study of two groups of patients suffering from idiopathic hypogonadotropic hypogonadism, with very low testosterone concentrations and decreased bone density (group I: mean age – 32±2 years, mean testosterone levels – 1.7±0.2 nM/l, fused epiphyses; group II: mean age - 21±1 years, mean testosterone levels – 1.4±0.4 nM/l, open epiphyses) revealed that testosterone treatment increased cortical bone density in both groups and trabecular bone density only in patients with open epiphyses [44]. Also in eugonadal men with vertebral crush fractures testosterone treatment for 6 months increased spinal BMD by 5%, and increased testosterone and estradiol levels by 55% and 45%, respectively, decreased sex hormone binding globulin by 20%, as well as decreased bone turnover markers. The change in BMD was significantly correlated with a change in serum estradiol but not with a change with serum testosterone [10]. Moreover, Ongphiphadhanakul et al. [45] have shown that BMD in normal

men is associated with both circulating estradiol and free testosterone when univariate analyses were used, but when the effect of estradiol was taken into account, free testosterone was no longer significantly related to BMD. The authors suggest that most of the observed effects of testosterone on bone are not direct but may be mediated through estrogens derived from androgens. Therefore testosterone is a promising treatment for men with idiopathic osteoporosis, acting to suppress bone resorption by a mechanism that may involve estrogens [10, 19, 41]. However, confirmation is required that the benefit of testosterone treatment in reducing fracture risk is higher than possible adverse effects in the longer term [19]. Especially, the risk of prostatic cancer needs to be considered in any cost-benefit analysis of this approach [7].

Results of the present study indicate that attention should be paid to testosterone deficiency in the young age in terms of the potential risk of decreased bone mineral density in the advanced age.

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