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ORIGINAL ARTICLE

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Predictors of bone mineral density in healthy males

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Abstract Osteoporosis (OP) is a growing health problem not only in women but also in men. It is well known that men lose bone during aging and are at risk for OP, but the risk factors for OP in men remain controversial. To assess determinants of bone mineral density (BMD) in the spine and femoral neck, 37 healthy men aged 43–73 years were measured using dual photon absorptiometry. Predictors of lumbar spine and femoral neck BMD were determined using multiple linear regression analysis. Backward elimination procedure was used to identify variables significantly related to BMD. The independent variables entered the regression model included age; body mass index (BMI); smoking history; alcohol intake; urinary calcium and hydroxyproline; and serum concentrations of osteocalcin, parathyroid hormone, testosterone, growth hormone, and cortisol. Backward regression analysis indicated that testosterone, cortisol, and BMI were significant predictors of BMD in the lumbar spine while testosterone, hydroxyproline, and osteocalcin were significant predictors of BMD in the femoral neck. Testosterone, cortisol, and BMI accounted for 44% of the total variance in lumbar spine BMD, and testosterone, hydroxyproline, and osteocalcin accounted for 20% of the total variance in femoral neck BMD. These observations suggest that testosterone, cortisol and BMI are determinants of lumbar spine BMD, while testosterone, urinary hydroxyproline, and osteocalcin are determinants of femoral BMD in healthy men.

Keywords Osteoporosis · Men · Bone mineral density

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Introduction

Osteoporosis (OP) in women has been extensively investigated in numerous studies, but male OP has received much less attention. It has been increasingly recognized that age-related bone loss in men is a significant health problem [1, 2]. Consequently it is important to understand the determinants of bone mineral density (BMD) in men, who have been less widely studied than women, to aid in prevention and treatment. There are only few studies concerning predictors of BMD in men available , and pathogenesis of primary OP in men has not been completely understood [2, 3]. Up to 40% of men with severe OP have no identifiable medical condition or risk factor associated with bone loss, and in such men with primary OP the pathogenesis of age-related bone loss is far from clear [4]. Many risk factors for reduced bone mass in men appear to be similar to those which influence bone mass in women, and low bone mass in men might be associated with low body mass index (BMI), physical inactivity, cigarette smoking, glucocorticoid therapy, vitamin D deficiency, and hypogonadism [1, 2, 3, 4, 5, 6, 7, 8]. In clinical situations, success in the prevention and treatment of OP depends on the recognition of these conditions. However, previous studies concerning the pathogenesis of primary OP in men give conflicting results [3].

The aim of this study was to determine the predictors of BMD and the relationship among biochemical parameters of bone turnover, hormonal and metabolic factors related to calcium homeostasis, and BMD in men.

Materials and methods

This study was conducted at Physical Medicine and Rehabilitation Department of Hacettepe University School of Medicine. Thirty-seven healthy male subjects (mean age 59.8 ± 6.8 years, range 43–73 years) were studied. All study subjects were ambulatory and physically and mentally normal. A history of hypogonadism or

past or present treatment with androgens were exclusion criteria. Subjects who were undergoing treatment with drugs that could interfere with bone and mineral metabolism were also excluded.

Fasting blood samples were collected in the morning between 0800 and 0900 hours from all subjects. Serum calcium (Ca), phosphate (P), creatinine, and alkaline phosphatase (AP) were determined by standard laboratory techniques. Serum osteocalcin (OC), testosterone (T), growth hormone (GH), parathyroid hormone (PTH), and cortisol levels were determined using commercially available radioimmunoassay kits. The 24-h urinary calcium and hydroxyproline excretion were also measured. It is well known that urinary hydroxyproline levels can be influenced by diet, and to avoid this influence the study subjects were instructed not to consume meat or gelatin-containing products for the 72 h prior to urine collection.

Each subject was evaluated by a questionnaire to collect data including age, smoking habits, alcohol consumption, and anthropometric variables (height, weight). Body mass index (BMI) was calculated in kg/m^2.

Bone mineral densities of lumbar spine and femoral neck were measured using dual photon absorptiometry (DPA) (Philips Osteotech 300). The precision error of DPA is 1–3% for the lumbar spine and the hip [9].

Predictors of lumbar spine and femoral neck BMD were determined using multiple linear regression analysis. Backward elimination procedure was used to identify variables significantly related to BMD. The independent variables entered the regression model included age; BMI; smoking history; alcohol intake; urinary calcium and hydroxyproline; and serum concentrations of OC, PTH, T, GH, and cortisol. Pearson's and Spearman's correlations were performed to find the relation between BMD and other parameters. The SPSS for Windows program was used for these statistical tests.

Results

Descriptive data of the study subjects are summarized in Table 1. Values of T, PTH, GH and bone turnover parameters in our male population were within normal limits. Twelve (32%) men were smokers, and moderate alcohol consumption was recorded in 5 (13%) men. Serum testosterone levels were negatively correlated with age ($r = -0.41$, $p < 0.05$) (Figure 1). Men with lower BMI had significantly lower bone mass in the lumbar spine ($r = 0.43$, $P < 0.05$) (Fig. 2). In addition, men with lower bone mass in the lumbar spine had significantly higher serum cortisol levels ($r = -0.33$, $P < 0.05$) (Fig. 3). All other hormones and bone turnover parameters did not correlate significantly with BMD. Backward regression analysis indicated that testosterone, cortisol, and BMI were significant predictors of BMD in the lumbar spine while testosterone, hydroxyproline, and osteocalcin were significant predictors of BMD in the femoral neck. Testosterone, cortisol, and BMI accounted for 44% of the total variance in lumbar spine BMD (Table 2); and testosterone, hydroxyproline, and osteocalcin accounted for 20% of the total variance in femoral neck BMD (Table 3).

Discussion

Understanding the causes, prevention, and treatment of OP is increasingly becoming one of the cornerstones of

Table 1 Clinical characteristics (mean ± standard deviation) of 37 subjects in the study. *BMI* body mass index, *BMD* bone mineral density

	Mean ± standard deviation
Age (years)	59.8 ± 6.8
BMI (kg/m^2)	26.4 ± 3.5
Serum calcium (mg/dl)	9.4 ± 0.5
Serum alkaline phosphatase (U/l)	87.9 ± 26.8
Serum osteocalcin (μg/l)	3.3 ± 1.4
Serum parathyroid hormone (pg/ml)	33.3 ± 11.6
Serum testosterone (ng/ml)	4.4 ± 1.9
Serum growth hormone (mU/l)	1.4 ± 0.8
Serum cortisol (μg/dl)	12.5 ± 5.6
Urinary hydroxyprolin (mg/l)	19.6 ± 9.8
Lumbar spine BMD (g/cm^2)	0.97 ± 0.10
Femoral neck BMD (g/cm^2)	0.76 ± 0.06

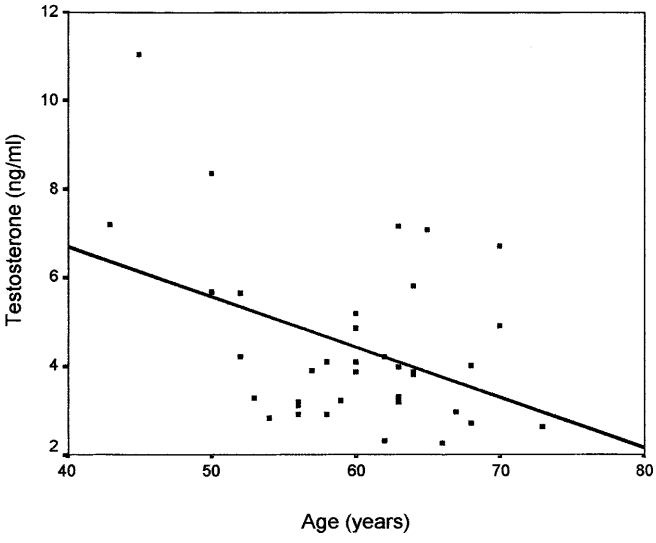

Fig. 1 Correlation between serum testosterone level and age of the study subjects ($r = -0.41$, $P < 0.05$)

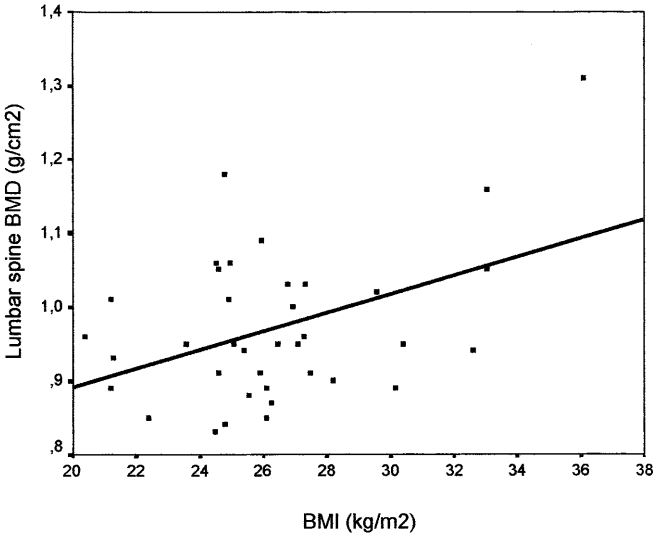

Fig. 2 Correlation between body mass index (BMI) and lumbar spine bone mineral density ($r = 0.43$, $P < 0.05$)

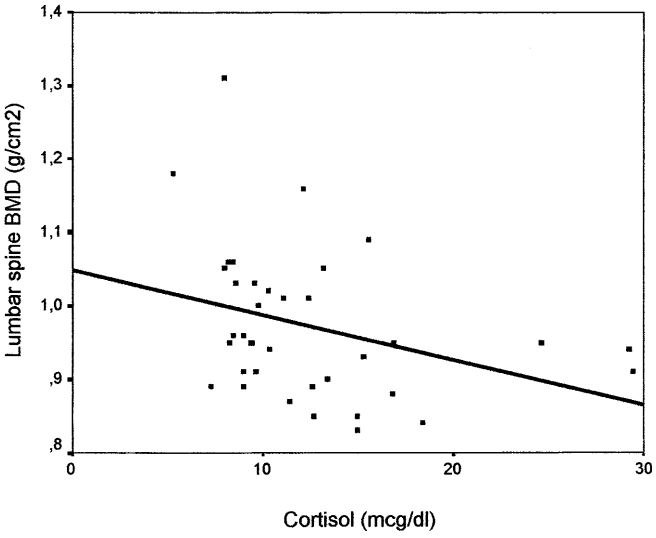

Fig. 3 Correlation between serum cortisol level and lumbar spine bone mineral density ($r = -0.33$, $P < 0.05$)

Table 2 Results of backward regression analysis for lumbar spine bone mineral density. *BMI* body mass index

Value	Coefficient ± standard error	*P* value
Intercept	0.55 ± 0.12	< 0.05
BMI (kg/m^2)	0.016 ± 0.004	< 0.05
Testosterone (ng/ml)	0.018 ± 0.007	< 0.05
Cortisol (μg/dl)	–0.007 ± 0.002	< 0.05
R^2	0.44	

Table 3 Results of backward regression analysis for femoral neck bone mineral density

Value	Coefficient ± standard error	*P* value
Intercept	0.78 ± 0.04	< 0.05
Testosterone (ng/ml)	0.017 ± 0.005	< 0.05
Osteocalcin (μg/l)	0.014 ± 0.008	< 0.05
Hydroxyprolin (mg/l)	–0.002 ± 0.001	< 0.05
R^2	0.20	

geriatric medicine. While much research effort and attention has been directed toward identification of risk factors for OP in women, there have been few studies aimed at examining OP in men [10]. Estrogen deficiency associated with menopause is the primary cause of the most rapid phase of bone loss in women. Men do not have a change comparable to menopause. However, both total and free testosterone decline gradually with age in men [11]. Similarly there was a negative correlation between age and testosterone levels in our study subjects. However, it is not clear whether the normal age-related decline in testosterone contributes to the bone loss. Although several studies have found testosterone to correlate with BMD in men, this finding has not been universal [11]. In this study we could not detect a correlation between BMD and serum testosterone levels, but testosterone concentration was found to be one of the predictors of BMD in the femoral neck and lumbar spine.

Markers of bone turnover have recently been studied as predictors of bone loss in post-menopausal women, but their relevance for bone loss in men remains uncertain [12]. In our study, urinary hydroxyproline and serum octeocalcin levels were found to be predictors of bone mass in the femoral neck.

Our study showed that BMI was associated with BMD in the lumbar spine and was negatively related to its subsequent loss. This finding is consistent with previous studies in men, which have also suggested that obesity is associated with increased BMD [10, 12]. This positive association has been attributed to adipose tissue because most estrogens in men come from the conversion of androgens to estrogens in adipose tissue [10].

Exogenous glucocorticoids are known to increase the risk of osteoporosis. However, far less is known of the contribution made by endogenous circulating cortisol levels to adult skeletal status. Dennison et al. reported an association between plasma cortisol concentration and BMD in men [13]. Similarly, in this study we have found plasma cortisol levels to be negatively correlated with lumbar BMD. Our results also indicate that cortisol is one of the main predictors of lumbar bone mass.

GH has also been implicated in the pathogenesis OP [11]. However, this issue remains controversial, as not all studies have demonstrated a relationship between GH and bone mass [11, 14]. Nor could we in our male population detect an association between GH and BMD.

The effects of smoking and alcohol use on osteoporosis in males have not been well established. Smoking has been implicated as a risk factor in one study [15], but in the present study, consistent with findings from several cross-sectional studies [10, 16 17, 18, 19], this relationship was not seen. Previous studies have shown an association between alcohol abuse and OP; other studies, on the other hand, have shown that moderate alcohol consumption may be associated with an increase in BMD [4, 19]. None of our subjects was alcoholic and only five men reported moderate alcohol consumption. It is thus not surprising that no association was found between alcohol use and BMD in this study.

Dual energy X-ray absorptiometry (DEXA) is currently considered the "gold standard" for BMD measurements. BMD measured by DPA might be considered as a limitation of this study. However, the reported precision error of DPA is very comparable to that of DEXA (1 to 3% and 0.5 to 3.2% respectively) for lumbar spine and femoral neck [9].

In summary, data in our male population indicate that testosterone, cortisol, and BMI were significant predictors of BMD in the lumbar spine while testosterone, hydroxyproline, and osteocalcin were significant predictors of BMD in the femoral neck. Because of the

small sample size, our findings suggest but cannot prove that these factors are the predictors of BMD. Longitudinal studies with larger numbers of subjects evaluating the change in BMD as a function of sex hormone levels and other risk factors would be valuable to further clarify relationships between possible risk factors and BMD in men.

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