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Risk Factors for Osteoporosis in Healthy Males

Research Article

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Abstract: We investigated the correlation of bone mineral density (BMD) with risk factors and laboratory parameters (e.g., markers of bone turnover, biochemical indicators, and hormonal factors) in males without secondary osteoporosis. A total of 105 males were divided into two groups: Group 1 (n: 52) <60 years, and Group 2 (n:53) ≥ 60 years. The subjects were evaluated for risk factors (European Vertebral Osteoporosis Study (EVOS) and BMD) and for biochemical (i.e., blood calcium, blood phosphorus, urinary calcium/phosphorus, creatinine clearance, osteocalcin, and deoxypyridinoline) and hormonal markers (follicle-stimulating hormone [FSH], luteinizing hormone [LH], free testosterone [fT], and parathyroid [PTH]) of bone mineral metabolism. In Group 1, no significant relationship was observed between risk factors for both lumbar and femoral neck BMDs and risk factors and laboratory parameters ($p>0.05$). On the other hand, we observed in Group 2 a significant positive correlation between lumbar BMD and BMI, BMI at 25 years of age, and fT; in the same group, a negative correlation between lumbar BMD and deoxypyridinoline ($p<0.05$) was seen. We saw a significant positive correlation between femoral neck BMD and BMI, BMI at 25 years of age, and daily activities of life in Group 2. In addition, we saw a negative correlation between femoral neck BMD and height difference, fT, LH, and deoxypyridinoline in Group 2 ($p<0.05$). Risk factors for male osteoporosis were multifactorial: demographic and clinical data (difference of height, BMI, physical activity) together with biochemical and hormonal data (deoxypyridinoline, fT, LH) were significant, and most of the risk factors analyzed were related to bone loss in the proximal femur.

Keywords: *Male • Osteoporosis • Risk factors*

1. Introduction

Osteoporosis, a major health issue that leads to fractures and progressive deterioration, is the most common bone metabolism disorder and, therefore, deserves greater emphasis on a global scale. Although studies report disparate results, approximately 200 million people are estimated to have osteoporosis [1]. In the United States, osteoporosis causes 1.5 million fractures that cost 13.8 billion dollars annually [2,3]. Approximately one-third of osteoporotic fractures occur in males [2]; one out of every four males over 60 years old suffers from an osteoporotic fracture [2].

Factors that will help to decrease the mortality and morbidity of osteoporosis and reduce treatment costs include identifying the risks, educating risk groups about those risks and complications, and providing the necessary medical treatment [4]. Although risk factors of osteoporosis for males are similar to those for females, male osteoporosis usually occurs due to secondary risk factors such as hypogonadism, aging, ethnicity, smoking, alcohol consumption, deficiency in dietary calcium intake, physical inactivity or sedentary lifestyle, low body mass index (BMI), certain diseases, and medications (particularly glucocorticoid use) [2,3]. Secondary factors may be discovered in as many as half of men with osteoporotic fractures, whereas only about 20% of women with such fractures will have an identifiable secondary cause [4,5]. Although many men diagnosed with osteoporosis have at least one identifiable secondary cause, the majority do not. Factors that contribute to bone loss in healthy men are less well understood. As male osteoporosis is multifactorial, risk factors other than secondary causes should be identified.

Although studies analyzing the risk factors of male osteoporosis exist in the literature [6-8], few assess the risk factors together with the analysis of bone biomarkers and laboratory parameters. Moreover, these studies are included small number of cases with

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higher mean age [6-8]. Therefore, we investigated the correlation of bone mineral density (BMD) with risk factors and laboratory parameters (e.g., markers of bone turnover, biochemical indicators, and hormonal factors) in males without secondary osteoporosis.

2. Material and Methods

Our study included 105 healthy, ambulatory, physically active male subjects aged between 37 and 80 who met the inclusion/exclusion criteria between January 2005 and December 2006. They were married to female patients who had been referred to Outpatient Clinics of Ege University School of Medicine for bone densitometry. Patients having other diseases that affect bone metabolism (i.e., endocrine, metabolic, renal, hepatic, rheumatologic) and using drugs that interfere with bone metabolism were excluded from the study. Systemic examination and examination of the locomotor system was performed for all patients. Body weights of the subjects were measured by electronic scale, and height was determined by a wall-mounted stadiometer. Body weight (kg), height (meter), difference of height (meter, height at the time of study – height at the age of 25), and BMI (kg/m^2, both at the time of study and at the age of 25) were calculated. All subjects were grouped as <60 years (Group 1, n = 52) or ≥ 60 years (Group 2, n = 53).

2.1. Assessment of Risk Factors and Nutrition

The European Vertebral Osteoporosis Study (EVOS) questionnaire was used to assess the risk factors [9]. The EVOS questionnaire is a validated, detailed questionnaire concerning health (health status, back pain), diet (calcium intake, dairy products consumption in different periods of life), lifestyle (alcohol consumption, smoking, physical activity [walking, cycling, and stair climbing]; and immobilization), medical history (patient/familial history of fractures), demographic data (marital status, education level), family history (history of fracture), and anthropometric data (weight, height, BMI). Questions related to gynecologic data were omitted as all participants of the study were male.

2.2. Bone Mineral Density Measurement (BMD)

BMD of the lumbar spine (L1–L4) and the proximal femur (femoral neck) was measured by dual-energy X-ray absorptiometry (DEXA) using a Hologic QDR 4500A apparatus (Hologic, Waltham, MA, USA). In our laboratory, the coefficient variation is 1.0% for both the lumbar spine and total femur sites. Results were expressed in g/cm^2.

2.3. Hormonal and Biochemical Markers

Blood and urine samples were collected from all patients after an overnight fast. Blood specimens were analyzed for creatinine, creatinine clearance, serum calcium, and phosphate, and 24-hour urinary calcium and phosphate were measured using standard automated techniques. Gonadal status was assessed by levels of follicile-stimulating hormone (FSH) and luteinizing hormone (LH) and of free testosterone (fT).

To monitor changes of bone turnover, biochemical markers were used. In this study, osteocalcin was used as a bone formation marker and deoxypyridinoline (DPD) as a bone resorption marker. Serum osteocalcin, FSH, LH, and fT were measured by immunometric assay (Immulite Analyzer, DPC's Technical Services Department, USA). Urine DPD, which is used to monitor type 1 collagen resorption, was measured by chemiluminescent enzyme-labeled immunoassay (Immulite Analyzer, Metra Biosystems, DPC's Technical Services Department, USA). Samples were stored at −70°C. Serum-intact parathyroid hormone (PTH) was measured by immunoradiometric assay (IDS, UK). The intra- and inter-assay variation coefficients were lower than 10% for all biochemical assays. The local committee of our institution approved the study, and all subjects provided written informed consent.

2.4. Statistical Analysis

All data were analyzed using the Statistical Package for the Social Sciences (SPSS) statistical software package, Version 13.0. Scored parameters were analyzed by the Spearman test and numerical parameters by the Pearson test. The *t*-test was used to compare the mean values of two groups, and one-way variance analysis was used for more than 2 groups. The Bonferronni test was performed for dual comparison if a statistically significant difference was determined by comparison of the mean values. A p value less than 0.05 was accepted as statistically significant.

3. Results

3.1. Demographic data and risk factors

Demographic data of the cases and risk factors for osteoporosis are presented in Table 1. The mean age for the study population was 59.24 ± 10.85, while it was 50.46 ± 6.61 for Group 1 and 67.85 ± 6.31 for Group 2.

Table 1. Demographic characteristics, risk factors of osteoporosis, level of physical activity, and calcium intake of the cases between Group 1 (<60 years) and Group 2 (≥ 60 years).

Demographic and Clinical Characteristics (n: 105)		Group 1 (n:52)	Group 2 (n:53)
BMI (kg/m^2) (Mean ± SD)		25.49±3.60	26.5±4.02
Marital status (married %)		94.2	94.3
Educational level (Mean ± SD)		12.08±3.34	10.09±3.39*
History of fracture (positive, %)		7.7	9.4
History of hip fracture in the family (positive, %)		5.8	9.4
Smoking (non-smokers, %)		28.2	30.2
Alcohol consumption (none, %)		38.5	52.8
Health status (good, %)		42.3	37.7
Back pain (present, %)		46.2	32.7
Physical Activity Level			
Walking or cycling (none, %)		11.5	13.2
Daily level of activities at different periods of life (moderate, %)			
	Age 15-25 years	46.2	41.8
	Age 25-50 years	55.8	58.5
	Age over 50 years	28.6	17.0
Daily level of activities at different periods of life (none, %)			
	Age 15-25 years	25.0	47.2
	Age 25-50 years	40.4	49.8
	Age over 50 years	89.5	94.3
Stair climbing/day (2 floors, %)		32.7	28.3
Calcium Intake			
Dairy products (none, %)			
	Solid cheese	32.7	41.5
	Soft cheese	57.7	46.7
	Yoghurt	3.8	3.8
	Milk	63.5	34.0
	Other	63.5	64.2
Consumed milk in different periods of life (less than one per week)			
	Age 15-25 years	55.8	47.2
	Age 25-50 years	57.7	49.1
	Age over 50 years	62.1	41.5

*SD: Standard deviation, BMI: body mass index, * p<0.05*

Comparison of demographic and risk factors between the two groups revealed no statistically significant difference except with respect to the duration of education (p>0.05). It was established that the duration of education of Group 1 was significantly higher than that of Group 2 (≥ 60 years) (p<0.05). In the two groups, nine patients (8.6%) had a fracture history.

3.2. Biochemical laboratory tests, hormonal tests, and BMD

Results of biochemical laboratory tests, hormonal tests, and BMD are presented in Table 2. A significant elevation of fT and creatinine clearance and significantly reduced levels of FSH and LH were observed in Group 1 as compared to Group 2 (p>0.05). Amounts of femoral neck BMD were significantly lower in Group 2 than they were in Group 1 (p<0.05).

3.3. Correlation of lumbar and femoral neck BMD with risk factors and laboratory parameters

A negative correlation was determined between age and the BMD of the femoral neck (r=-0.34) (p<0.05). Other significant correlations were presented in Table 3. No significant relationship was observed between either lumbar or femoral neck BMD and risk factors and

Table 2. Hormonal, biochemical, and BMD results of Group 1 (<60 years) and Group 2 (≥ 60 years).

Hormonal Variables	Group 1 (n:52)	Group 2 (n:53)
Östradiol (pg/ml)	25.76±14.48	26.66±4.02
Cortisol (mcg/dl)	16.20±5.69	16.61±4.82
PTH (pg/ml)	29.06±14.90	32.30±15.25
Free testosterone (pg/ml)	16.86±5.69	12.75±7.06*
FSH (mIU/ml)	4.65±2.82	7.02±3.90*
LH (mIU/ml)	4.68±4.27	7.30±8.86*
Deoxypyridinoline (nM/mM)	4.14±1.14	5.08±2.27*
Osteocalcine (ng/ml)	7.13±4.97	5.68±3.56
Biochemical Results		
Ca (mg/dl)	9.29±0.89	9.41±0.51
P (mg/dl)	3.29±0.51	3.67±2.80
Creatinine clearance (ml/dk)	93.48±33.71	72.54±26.73*
Ca/24 h. urine (mg/24 h)	201.32±103.38	189.71±97.48
P/24 h. urine (mg/24 h)	806.98±339.12	703.11±322.32
Blood glucose (mg/dl)	105.00±35.89	114.96±36.08
BMD Results		
Lumbar BMD (g/cm^2)	0.92±0.14	0.95±0.18
Femoral neck BMD (g/cm^2)	0.77±0.14	0.71±0.10*

*PTH: parathyroid hormone, FSH: follicle-stimulating hormone, LH: luteinizing hormone, Ca: calcium, P: phosphate, BMD: bone mineral density, * p<0.05*

Table 3. Correlation of lumbar and femoral neck BMD with risk factors and laboratory parameters in Group 1 (<60 years) and Group 2 (≥ 60 years).

	Lumbar BMD		Femoral Neck BMD	
Risk Factors	Group 1	Group 2	Group 1	Group 2
BMI (kg/m^2)	0.13	0.46*	0.23	0.56*
BMI at age 25 (kg/m^2)	0.10	0.32*	0.26	0.38*
Difference of height (cm)	-0.12	-0.21	-0.19	-0.28*
Daily activities of life	0.06	0.07	0.19	0.38*
Laboratory Parameters				
Free testosterone (pg/ml)	-0.02	0.34*	0.18	-0.31*
LH (mIU/ml)	-0.09	-0.23	-0.15	-0.31*
Deoxypyridinoline (nM/mM)	-0.21	-0.38*	-0.04	-0.39*

** p<0.05, BMD: bone mineral density, BMI: body mass index kg/m^2, LH: luteinizing hormone*

laboratory parameters in Group 1 (p>0.05) In Group 2, there was a significant positive correlation between lumbar BMD and BMI, BMI at the age of 25, and fT. In addition, a significant negative correlation was seen in Group 2 between lumbar BMD and DPD (p<0.05). In Group 2, there was a significant positive correlation between femoral neck BMD and BMI, BMI at the age of 25, and daily activities of life (p<0.05). In addition, there was a negative correlation in Group 2 between femoral neck BMD and height difference, fT, LH, and DPD (p<0.05). No significant correlation was observed between other parameters (demographic and clinical [marital status, education level, history of hip fracture in the family, smoking, alcohol intake, health status, back pain]; diet [calcium intake]; bone formation [osteocalcine]; hormonal variables [estradiol, cortisol, PTH, FSH]; biochemical variables [ALP, calcium and phosphorus levels, creatinine clearance, urinary calcium and phosphorus, blood glucose]) and lumbar and femoral neck BMD in either group (p>0.05).

4. Discussion

In our study, risk factors that cause bone loss in healthy males were multifactorial, and most of the risk factors analyzed were associated with bone loss in the femoral neck. Of the skeletal sites measured, only BMD of the femoral neck declined with age [6]. In their study, Dubbo *et al*. determined an annual bone loss of 0.82% in the femoral neck of males who were between 30 and 80 years old [10]. We also determined age-related loss in the femoral neck as reported in other studies, but BMD of the lumbar region did not show any correlation with age [2,6], which may be due to spinal osteoarthritis, calcification of the aorta, and other causes of ectopic calcification [2,6]. It is also reported that bone loss may be better detected by lateral rather than antero-posterior projection [6]. Our use of antero-posterior projection for the lumbar region may have contributed to our failure to determine age-related bone loss.

BMI was positively correlated with BMD [3]. Studies have shown that lower BMI scores were associated with BMD loss [3,11]. In their meta-analysis, De Laet *et al*. reported that lower BMI alone increased hip fracture risk apart from age and gender [12]. In our study, we determined that current BMI and BMI at the age of 25 were associated with BMD of the femoral neck and lumbar region as similarly reported in previous studies [7,8,13]. Height loss has been shown to be an indicator of incident vertebral fractures [14]. However, the relationship between height loss and BMD in different skeletal regions has not yet been firmly established, and the imperfection of human memory to recall height loss throughout the life span must also be considered. In our study, we determined that height loss was correlated with BMD of the femoral neck similar to other studies [14,15].

The risk of vertebral fracture increases approximately twofold for each decrease in SD in the BMD of the lumbar spine and femoral neck [16]. The risk of any type of fracture is generally considered to increase 1.5-fold for each decrease in SD of BMD measured at any body part [17]. In our study, we did not observe a correlation between fracture history and BMD of the femoral neck and lumbar, which may be attributed to the lower incidence of fracture history in the study group and an inability to perform statistical analysis for such a low value.

Physical activity plays an important role in achieving peak bone mass during adolescence and is positively associated with BMD in adult males [3,18]. In their study, Lunt *et al*. determined that both current and lifetime physical activity were positively correlated with BMD. However, this effect was more prominent for hip BMD than for spinal BMD [18]. Similar to these studies, we determined that daily activities of life were positively correlated with hip BMD in elderly males over the age of 60.

Adequate intake of calcium is necessary to achieve optimal peak bone mass during development and to maintain calcium homeostasis [3]. Although a number of studies have suggested that higher calcium intake is associated with lower rates of bone loss [19-21], several studies, including ours, failed to establish an association between lower calcium intake and osteoporosis [22,23]. Therefore, we believe that further studies that stringently assess calcium intake are necessary.

End-stage renal disease dialysis patients have reduced BMD and higher rates of hip fracture [24]. Creatinine clearance in particular has been reported to determine bone loss of 4 years [25]. In the present study, creatinine clearance levels never decreased in any subject to an extent that could result in renal failure. Therefore, the decrease in creatinine clearance in men over 60 years old may not have been reflected in BMD. Decrease of BMD in patients with renal failure has been attributed to an increase in PTH and a decrease in 1.25 dihydroxyvitamin D caused by their impaired renal function [25,26]. In our study, we did not measure vitamin D levels, one of the causes for secondary hypoparathyroidism, and this may be considered a limitation of our study. However, the mean PTH levels seen in our study were within normal limits, thereby excluding the possibility of secondary hyperparathyroidism. We did not determine an association between PTH levels and BMD of the lumbar region and the femoral neck.

It is not clear whether bone turnover markers can be used to assess BMD changes in healthy men [7]. A number of studies, primarily with women, suggest that the association between bone turnover markers and change in BMD ranges from non-significant [27] or weak [28] to moderate association [29]. Cross-sectional studies in men have demonstrated that markers of bone formation decrease with advancing age, but they were negatively correlated with BMD [30,31]. A prospective study, again involving elderly men, has demonstrated that increases in either bone formation or bone resorption markers were associated with an increased loss in BMD of the femoral neck [32]. In our study, the bone resorption marker DPD was found to be associated with BMD of both the lumbar region and the femoral neck.

It has been recognized that estrogen plays a crucial role in the maintenance of bone mass in women. Although men do not experience such sudden reductions in sex hormone levels [33], they experience substantial age-related decreases in BMD [33], testosterone, estradiol,

and gonadotropines levels [2]. Hypogonadism, either primary or secondary, is known to be a risk factor for male osteoporosis [33]. Studies have demonstrated the association of testosterone with hip and femoral neck BMD [7,8,34,35]. We also determined a significant association between femoral neck/lumbar BMD and levels of fT.

Smoking is recognized as a risk factor, and a history of smoking has been reported to increase the risk of hip fractures [36]. However, there are numerous studies similar to ours that failed to reveal an association between smoking and BMD [37,38]. Excess alcohol intake has been reported to cause osteoporosis and increase the risk of hip fractures [39]. In our study, the lack of association between BMD and alcohol may be due to minimal or no alcohol consumption by the subjects.

Absence of lateral DEXA projection, measurement of vitamin D levels, and a relatively small number of patients may be considered limitations of our study. Additionally, we used a cross-sectional design and enrolled volunteer participants for the study rather than randomly select subjects from the general population. Many of the variables examined were derived from subjects' recall rather than from direct observation. In addition, we examined these relationships only in the Turkish population; therefore, our findings may not be applicable to other groups since they do not adequately address the potential influence of ethnicity in our study. However, many of the correlations observed showed similarities with previous studies on male osteoporosis. Comparison of both hormonal and biochemical results together with all risk factors and a wide age range of subjects may be advantages of our study compared to others. Further studies that provide long-term analysis of factors that cause osteoporosis in healthy males are required.

In conclusion, risk factors of male osteoporosis are multifactorial, and demographic and clinical data (BMI, BMI at the age of 25, difference of height, physical activity) as well as biochemical and hormonal data (DPD, fT, LH) were determined to be significant. Most of these risk factors were found to be associated with bone loss in the proximal femur**.** The present study underlines that (1) ideal body weight and physical activity in particular have an important impact on bone loss and (2) hormone tests (free testosterone) are essential for those patients who are diagnosed with osteoporosis. In this respect, strategies to prevent bone loss and osteoporosis in Turkish men should include lifestyle modification and maintenance of hormone levels. Longitudinal studies that include larger numbers of patients are required to validate our results. Risk factors determined in our study may facilitate prevention, early diagnosis, and treatment of osteoporosis as well as to avoid complications that may arise. These findings may assist in the clinical and epidemiologic identification of men who require enhanced diagnostic and therapeutic efforts for prevention and treatment of osteoporosis.

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