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The relationship between sex steroids, bone turnover and vertebral fracture prevalence in asymptomatic men ☆

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ABSTRACT

Objective: To examine the association between oestradiol (E2), testosterone (T), SHBG levels and vertebral fractures' (VFs) prevalence in asymptomatic men.
Methods: The study cohort consists of a population of 112 consecutive men (mean ± SD (range) age, weight and BMI were 62.9 ± 9.2 (41–84) years, 75.0 ± 13.8 (45–120) kgs and 26.4 ± 4.7 (18.0–39.6) kg/m^2, respectively). Lateral vertebral fracture assessment (VFA) images and scans of the lumbar spine and proximal femur were obtained using a GE Healthcare Lunar Prodigy densitometer. VFs were defined using a combination of Genant semiquantitative approach and morphometry. Serum levels of T, E2, CTx and osteocalcine were measured. Free androgen index (FAI) and free estradiol index (FEI) were calculated respectively from the ratio of serum T and E2 to SHBG.
Results: Among the 112 men, 38 (33.9%) had densitometric osteoporosis, and on VFA, VFs were identified in 60 (53.5%): 24 men had grade 1 and 36 had grade 2 or 3 VFs (32.1%). Men with VFs weighted less and had a statistically significant lower lumbar spine and total hip BMD and T-scores than those without a VFA-identified vertebral fracture. Levels of osteocalcine, CTx, and SHBG were statistically higher in men with grades 2 and 3 VFs than men with grade 1 VFs and those without VFs whereas FAI and FEI levels were significantly lower. Comparison of patients according to quartiles of SHBG levels showed that men in the highest quartile were older, had a lower lumbar spine and total hip BMD and a higher prevalence of osteoporosis and VFs. They had also higher levels of CTx. Stepwise regression analysis showed that the osteoporotic status and SHBG was independently associated to the presence of VFs.
Conclusion: Men with asymptomatic densitometric VFs have lower BMD than subjects without VFs. They have evidence of higher SHBG levels and hence lower free sex steroids as well as increased bone resorption. This study confirms that BMD and CTx are the most important determinant of asymptomatic VFs, and that SHBG is an independent risk factor that must be taken into account.

Introduction

The social and economic burden of osteoporotic fractures is an increasing public health concern both in men and women. As it is the case for women, aging in men is associated with bone loss. However, unlike in women where estrogen (E) deficiency at menopause is an established cause of osteoporosis, relative role of testosterone (T) and E in bone loss in men is not clear [1]. Male hypogonadism has been associated with osteoporosis and T therapy is accompanied by increased bone formation. A few studies have reported an age associated decline in serum T levels and its free fractions as well as a positive association between the decreases in serum T and its free fractions with bone mineral density (BMD); however, other studies have failed to confirm these observations [2,3]. A role for E has been suggested in the development and maintenance of the male skeleton. E levels have been shown to be decreased in male osteoporotic patient compared to age-matched controls.

Sex hormone-binding globulin (SHBG) is a plasma glycoprotein that binds with high affinity to sex steroids, thereby regulating their bioavailability and access to target cells [4]. High SHBG was significantly associated with the risk of clinical vertebral fractures (VFs) [5] and nonvertebral fractures [6] in recent studies. A weak but significant association was found between SHBG and the risk of proximal femoral fracture (HR, 1.52; 95%CI, 1.0–2.31; $P<0.05$) but was abolished after adjustment on various confounders. The incidence of nonvertebral fractures was higher in men who had SHBG levels in the highest tertile and BMD values in the lowest tertile (17/1000 person-years) [6]. In the vast MrOS Swedish cohort of 2639 men having a mean age of 75 years,

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high SHBG was significantly associated with the risk of fractures at any site (HR, 1.41; 95%CI, 1.22–1.63; $P<0.05$) and the association persisted after adjustment on age [7]. The data from the Dubbo cohort of 609 men [8] showed that the risk of postfracture death was increased two-fold in individuals with SHBG levels greater than 7.2 μg/ml, undetectable testosterone, advanced age, or low BMD.

For both men and women, VFs adversely affect quality of life [9]. Moreover, the presence of a prior VF is a strong independent risk factor for future vertebral and non-vertebral fractures [10]; thus, knowledge of VF status is important for fracture risk estimation [11]. Since many VFs are not recognized clinically, vertebral morphometry using dual-energy X-ray absorptiometry (DXA) also known as vertebral fracture assessment (VFA) is a fast, low-radiation technique which produces images that are of sufficient quality to be used to diagnose the presence of vertebral deformity consistent with fracture [12]. VFA can aid in identifying those who may not otherwise be considered at high risk for fracture [13,14].

Knowing clinical and biological risk factors that contribute to the risk of fractures is crucial to understand better the multifactorial pathogenesis of the disease and to better define the population of patients at risk that need to be treated [15]. Indeed, although BMD has been used to define osteoporosis, about of half of fragility fractures occur in women and men with a BMD level above the WHO threshold of osteoporosis [16]. The influence of sex steroids on asymptomatic VFs have never been evaluated before. Thus, we aimed to examine the relationship between circulating levels of E, T, SHBG levels and bone turnover markers and the prevalence of VFs in a cohort of asymptomatic men who had a VFA examination during their BMD testing.

Material and methods

Subjects

One hundred and twelve consecutive men who had no previous diagnosis of osteoporosis were entered into the study. Men were recruited prospectively through advertisements and "word of mouth" between December 2009 and August 2010. Original inclusion criteria were age >50 and no previous osteoporotic fracture. Men with liver or renal disease, endocrine or metabolic abnormalities, and receiving medicine known to influence bone mineralization, such as corticosteroids, heparin, anticonvulsants, vitamin D, and bisphosphonates, were excluded. Our institutional review board approved this study. The procedures of the study were in accordance with the Declaration of Helsinki, and local ethics committee approval was obtained for the study. All the participants gave an informed and written consent. Each subject completed a standardized questionnaire designed to document putative risk factors of osteoporosis. Height and weight were measured in our center before DXA measurement, in light indoor clothes without shoes. Body mass index (BMI) was calculated by dividing weight in kilograms by height in meters squared.

BMD measurement

BMD was determined by a Lunar Prodigy Vision DXA system (Lunar Corp., Madison, WI). The DXA scans were obtained by standard procedures supplied by the manufacturer for scanning and analysis. All BMD measurements were carried out by 2 experienced technicians. Daily quality control was carried out by measurement of a Lunar phantom. At the time of the study, phantom measurements showed stable results. The phantom precision expressed as the coefficient of variation percentage was 0.08. Moreover, reproducibility has been assessed in clinical practice and showed a smallest detectable difference of 0.04 g/cm^2 (spine) and 0.02 (hips) [17]. Patient BMD was measured at the lumbar spine (anteroposterior projection at L1–L4) and at the femurs (i.e., femoral neck, trochanter, and total hip). The World Health Organization (WHO) classification system was applied, defining osteoporosis as T-score ≤ -2.5 and osteopenia as $-2.5<$T-score<-1. Study participants were categorized by the lowest T-score of the L1–4 lumbar spine, femur neck, or total femur.

VFA was classified using a combination of Genant semiquantitative [18] (SQ) approach and morphometry in the following manner: each VFA image was inspected visually by two clinicians (IG and AM who had a previous training session in VFA) to decide whether it contained a fracture in any of the visualized vertebrae. Each vertebra that was judged as fractured by visual inspection by any of the investigators was measured using built-in morphometry and assigned a grade based on Genant SQ scale, where grade 1 (mild) fracture is a reduction in vertebral height of 20–25%, grade 2 (moderate) a reduction of 26–40%, and grade 3 (severe) a reduction of over 40%.

Biological measurements

All subjects had fasting blood taken in the morning. The samples were frozen and stored at −20 °C and subsequently thawed and analyzed in one batch. Serum T, oestradiol (E2), SHBG, osteocalcine and crosslaps (CTx) were measured by electrochemiluminescent immunoassay (ECLIA) technique (Cobas e601, Roche Diagnostics GmBH, Mannheim, Germany). All the laboratory tests were subject to validation using National External Quality Assurance Schemes. Free androgen index (FAI) was calculated from the ratio of serum testosterone to SHBG to give an estimate of the free circulating concentration. Similarly, the free oestradiol index (FEI) was calculated from the ratio of serum E2 to SHBG.

Statistical analysis

Results are presented as means (SD) and categorical variables are expressed as frequencies. To compare patients with and without vertebral fractures and according to the quartiles of SHBG levels, analysis of variance ANOVA was used. Correlations between continuous variables were calculated using Pearson correlation coefficients. Potential risk factors were entered to a stepwise conditional binary regression analysis and the resulted odds ratios with 95% confidence intervals were reported. The level for significance was taken as $P\leq 0.05$. Excel 2007 and SPSS 15.0 were used for statistical analysis.

Results

Patient demographics

In this cohort of 112 men, the mean ± SD (range) age, weight and BMI were 62.9 ± 9.2 (41–84) years, 75.0 ± 13.8 (45–120) and 26.4 ± 4.7 (18.0–39.6) kg/m^2, respectively (Table 1).

Among the 112 men, 38 (33.9%) had densitometric osteoporosis (T-score below −2.5 at the lumbar spine, the femoral neck or the total hip site). On VFA, 70% of vertebrae from T4 to T7 and 98% from T8 to L4 were adequately visualized. Vertebral fractures were identified using VFA in 60 (53.5%): 24 men had grade 1 and 36 had grade 2 or 3 VFs (32.1%). Fractures were most common in the mid-thoracic spine and at the thoraco-lumbar junction. As would be expected, the prevalence

Table 1
Characteristics of the population study (n = 112).

	Mean (SD)	Range
Age (years)	62.9 (9.2)	50–84
Weight (kg)	75.0 (13.8)	45–120
Height (m)	1.68 (0.1)	1.54–1.85
BMI (kg/m²)	26.4 (4.7)	18.0–39.6
Lumbar spine BMD (g/cm²)	1.026 (0.2)	0.610–1.545
Total hip BMD (g/cm²)	0.914 (0.1)	0.530–1.273
Lumbar spine T-score (SD)	−1.3 (1.5)	−4.8–2.9
Total hip T-score (SD)	−0.6 (1.1)	−3.9–1.8

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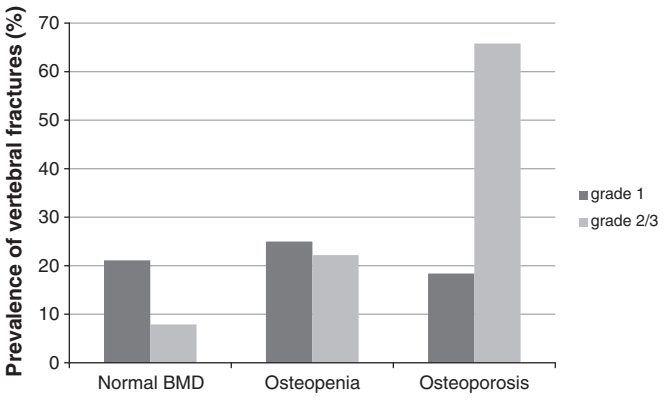

Fig. 1. Vertebral fracture prevalence (%) based on BMD.

of VFA-detected fractures was higher (P<0.0001) in men with lower BMD (Fig. 1).

Osteoporotic men were older and had a statistically significant lower weight, height and higher levels of CTx, E2, T, and SHBG than the other groups (osteopenia and normal BMD).

Men with VFs weighted less and had a statistically significant lower lumbar spine and total hip BMD and T-scores than those without a VFA-identified vertebral fracture (Table 2). Concerning the biological parameters, levels of osteocalcine, CTx, and SHBG were statistically higher in men with grades 2 and 3 VFs than men with grade 1 VFs and those without VFs whereas FAI and FEI levels were significantly lower.

Comparison of patients according to quartiles of SHBG levels showed that men in the highest quartile were older, had a lower lumbar spine and total hip BMD and a higher prevalence of osteoporosis and VFs (Table 3) (Fig. 2). They had also higher levels of CTx.

The results of correlations between the biochemical data and age, BMI and BMD are shown in Table 4. There was a significant positive correlation between CTx values osteocalcine and SHBG and significant negative correlation with total hip BMD. SHBG was positively correlated to age and negatively to BMI and BMD (lumbar spine and total hip).

Stepwise multiple logistic regression analysis was therefore performed to determine the combination of variables that accounted for the greatest proportion of variance in BMD at each site (Table 5). BMI was the best predictor of BMD at all sites. SHBG was significantly related to lumbar spine BMD whereas CTx was related to total hip BMD. Stepwise multiple logistic regression analysis was repeated using the combined data to determine the combination of variables that best predicted garde 2/3 VFs (Table 6). The best model comprised the osteoporotic status, CTx levels and SHBG.

Table 3
Comparison between patients according to quartiles of SHBG.

	Quartile 1 N = 47	Quartile 2 N = 47	Quartile 3 N = 48	Quartile 4 N = 46	P
Age (years)	59.2 (1.8)	61.8 (1.4)	65.0 (1.5)	67.7 (1.6)	0.002
Total hip BMD (g/cm²)	0.996 (0.3)	0.928 (0.3)	0.903 (0.3)	0.822 (0.3)	0.002
T-score total hip (SD)	−0.03 (0.1)	−0.5 (0.2)	−0.5 (0.2)	−1.3 (0.2)	<0.0001
Lumbar spine BMD (g/cm²)	1.101 (0.3)	1.077 (0.3)	1.017 (0.2)	0.908 (0.2)	<0.0001
T-score lumbar spine (SD)	−0.7 (0.2)	−0.9 (0.2)	−1.3 (0.2)	−2.3 (0.2)	0.001
Prevalence of osteoporosis (%)	17.9	28.6	28.6	60.7	0.001
Prevalence of grade 2/3 VFs (%)	17.9	21.4	32.1	57.1	0.001
CTx (pg/ml)	0.471 (0.3)	0.428 (0.2)	0.652 (0.6)	0.836 (0.7)	0.018
Osteocalcine (ng/ml)	22.9 (23.9)	21.3 (12.1)	28.0 (33.9)	36.3 (53.1)	NS

Discussion

We found that a high level of SHBG is a risk factor for osteoporosis and asymptomatic VFs in a cohort of men with a broad age range. SHBG independently predicted low BMD at the lumbar spine level and VFs. The fracture subjects did have significantly higher SHBG levels and consequently significantly lower FAI and FEI, as well as evidence of increased bone resorption (as shown by higher levels of CTx). It is worth noting that the association between SHBG levels and VF prevalence was stronger with grade 2/3 than with grade 1.

These results are consistent with other studies in healthy subjects, which all reported sex steroids and/or SHBG to be predictors of BMD. Diaz-Guerra et al. [19] found that SHBG, PTH and weight were independent predictors of BMD, which together accounted for 24–40% of the variability in BMD dependent on the site chosen. The majority of this variability was accounted for by weight. There is also good evidence to support the role of sex steroids in regulating bone turnover. Leder et al. [20] showed in young men aged 20–44 years (where Goserelin was used to block the production of all sex steroids, and were then replaced with testosterone patches with and without anastrazole, to block aromatization to E2) that both T and E2 were required to normalize bone resorption. In terms of bone formation, T seemed to be more important than E2.

Table 2
Comparison between patients with and without vertebral fractures (VFs).

	Patients without prevalent VF N = 52	Patients with prevalent grade 1 VF N = 24	Patients with prevalent grade 2 and 3 VF N = 36	P
Age (years)	62.3 (8.7)	64 (7.5)	64.7 (9.0)	NS
Weight (kg)	79.1 (14.2)	75.8 (13.6)	69.1 (11.3)	0.003
Height (m)	1.69 (0.05)	1.68 (0.06)	1.66 (0.06)	NS
BMI (kg/m²)	27.4 (4.6)	26.8 (4.5)	24.9 (3.4)	0.02
Osteocalcine (ng/ml)	22.6 (18.3)	19.5 (8.7)	38.8 (54.5)	0.04
CTx (pg/ml)	0.418 (0.2)	0.441 (0.2)	0.959 (0.7)	<0.001
Estradiol (pg/ml)	19.7 (7.7)	24.9 (12.6)	26.8 (11.5)	NS
Testosterone (ng/ml)	3.9 (1.5)	4.6 (2.0)	4.5 (2.0)	NS
SHBG (nmol/l)	47.2 (21.2)	54.7 (21.2)	69.9 (31.1)	<0.001
FEI	0.23 (0.1)	0.17 (0.1)	0.14 (0.1)	0.003
FAI	31.7 (12.9)	28.8 (9.5)	24.7 (10.8)	0.02
Total hip BMD (g/cm²)	0.965 (0.17)	0.951 (0.15)	0.810 (0.15)	<0.001
Total hip T-score (SD)	−0.1 (1.0)	−0.4 (0.9)	−1.3 (1.1)	<0.001
Lumbar spine BMD (g/cm²)	1.125 (0.14)	1.060 (0.18)	0.889 (0.15)	<0.001
Lumbar spine T-score (SD)	−0.5 (1.1)	−1.0 (1.5)	−2.4 (1.2)	<0.001

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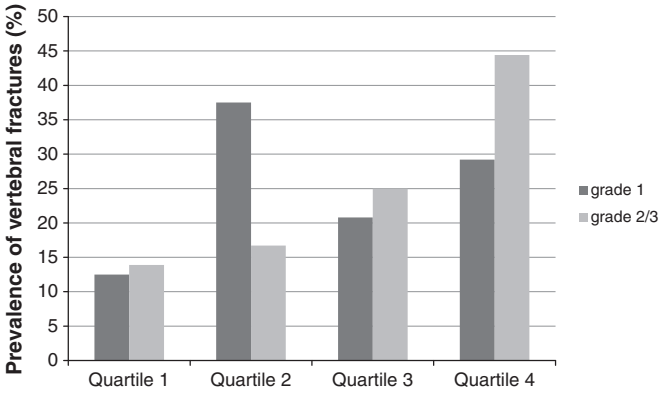

Fig. 2. Prevalence of vertebral fractures according to quartiles of SHBG levels (P>0.05 for all the parameters) 0.

Several other case–control studies have demonstrated no difference in total sex steroids, but significantly higher SHBG and lower FAI in osteoporotic men. Although these studies were all relatively small, they have been confirmed by larger cross-sectional and longitudinal studies. Legrand et al. [21] found SHBG to be a significant predictor of BMD. Center et al. [22] found SHBG, vitamin D and BMD to be independent predictors of fracture risk in 437 community dwelling men, of whom 54 had sustained low trauma fractures. There was a doubling of fracture risk for each standard deviation increase in SHBG and the combination of low SHBG, vitamin D and BMD resulted in a 30 fold increased risk of fracture.

The ability of androgens and estrogens to predict fracture risk in older men remains unresolved. Cross-sectional studies reported inverse associations between both serum E2 and T and prevalent fractures [5,23,24]. The predictive role of serum E2 and T for fracture risk in prospective studies remains contradictory [25]. These conflicting results might be explained by the fact that these prospective studies were underpowered, as they included few incident fractures.

Recently, Mellstrom et al. [26] analyzed the predictive role of serum E2 and T levels for incident fracture risk in the Osteoporotic Fractures in Men (MrOS) Sweden study and showed that both serum E2 and T levels were inversely associated with risk of all fractures (including fractures at the hip, distal radius, proximal humerus and pelvis, and clinical VFs) when analyzed separately. Also, serum SHBG levels have been shown to be directly related to prevalent fractures in men. In the MrOS Sweden study, men with high serum levels of SHBG have an increased risk of fracture (HR per SD increase 1.41, 1.22–1.63), confirming previous findings in the Tromso study [6] and the Dubbo Osteoporosis study [8]. Interestingly, both low E2 and high SHBG independently predicted risk of fractures in the MrOS Sweden study, with the highest fracture risk seen in men with both low E2 and high SHBG.

Most of the previously published studies evaluated the incident risk of hip fracture and few of them included clinical VFs. The spine is a key fracture site [27]; however, it has been estimated that only 30% of VFs receive clinical attention (which means that the majority of patients with VFs remain undetected) [28,29]. It appears that only those patients with the most severe vertebral fractures come to clinical attention (it is likely that this is due to higher levels of back pain and disability). Our study is the first to our knowledge to evaluate the influence of sex steroids on asymptomatic VF prevalence and the relationship with bone turnover markers.

SHBG plays a pivotal role in bone remodeling as it binds with high affinity to sex steroids, thereby regulating their bioavailability and access to target cells. Binding of SHBG to its specific membrane receptor

Table 5
Multiple regression analysis with BMD as dependent variable and all anthropometric and biochemical data entered.

	B	SE	Beta	t	p
LS BMD					
SHBG	−0.002	0.001	−0.255	−2.592	0.011
CTx	−0.014	0.030	−0.040	−0.458	0.648
Age	−0.003	0.002	−0.133	−1.428	0.156
BMI	0.012	0.004	0.272	2.997	0.003
TH BMD					
SHBG	−0.001	0.001	−0.145	−1.570	0.119
CTx	−0.065	0.027	−0.199	−2.447	0.016
Age	−0.003	0.002	−0.174	−2.006	0.047
BMI	0.015	0.003	0.361	4.239	0.000

LS BMD: lumbar spine bone mineral density; TH BMD: total hip bone mineral density.

Table 6
Multiple logistic regression analysis with fracture or no fracture (grade 2/3) as dependent variable and all anthropometric, BMD and biochemical data entered.

	Exp (B) 95% CI	P
T-score (lumbar spine or total hip) ≤−2.5	13.15 [3.75–46.17]	<0.0001
CTx	8.95 [1.78–44.87]	0.008
SHBG	1.02 [1.01–1.04]	0.048

Table 4
Correlation between biochemical values and age, BMI and BMD.

		Osteocalcine	CTx	SHBG	FEI	FAI	Age	BMI	LS BMD
CTx	r	0.605[a]							
	p	0.0001							
SHBG	r	0.128	0.213[b]						
	p	0.233	0.046						
FEI	r	−0.010	−0.067	−0.354[a]					
	p	0.923	0.537	0.001					
FAI	r	−0.124	−0.197	−0.355[a]	0.164				
	p	0.252	0.066	0.001	0.128				
Age	r	−0.030	−0.036	0.435[a]	−0.112	−0.223[b]			
	p	0.782	0.737	0.0001	0.297	0.037			
BMI	r	−0.215[b]	−0.191	−0.374[a]	0.360[a]	0.136	−0.211[b]		
	p	0.045	0.074	0.0001	0.001	0.207	0.048		
LS BMD	r	−0.102	−0.186	−0.420[a]	0.276[a]	0.289[a]	−0.271[b]	0.378[a]	
	p	0.345	0.083	0.0001	0.009	0.006	0.011	0.0001	
TH BMD	r	−0.358[a]	−0.312[a]	−0.426[a]	0.238[b]	0.212[b]	−0.331[a]	0.488[a]	0.647[a]
	p	0.001	0.003	0.000	0.026	0.048	0.002	0.0001	0.0001

BMI: body mass index; LS BMD: lumbar spine bone mineral density; TH BMD: total hip bone mineral density.
[a] Correlation is significant at the 0.01 level (2-tailed).
[b] Correlation is significant at the 0.05 level (2-tailed).

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regulates the intracellular transduction of sex-steroid signals, independently from the levels of sex steroids [4]. Recent data show that low androgen levels appear to give a synergistic contribution to fracture risk. The latter could derive from their key regulating role in preserving trabecular bone microarchitecture, as like as from their non-skeletal effects, such as effects on muscle mass and strength, cognition, balance, and, consequently, risk of falls [30]. The contributing role of low androgens would be namely displayed in the setting of high SHBG, which could either amplify the effects of sex steroids deficiency, or be a marker of non-skeletal factors, as frailty and nutrition status, also influencing fracture risk [31,32]. Thus, despite an additional effort and cost, in everyday practice, assaying serum SHBG may help to predict the severity of osteoporosis and VF risk in elderly men.

Our study has strengths and limitations. All of DXA and biochemical measurements were conducted with a single bone densitometer and a single biochemistry laboratory, with very careful quality controls in place. The assessment of fracture was carefully conducted using standard procedures of acquisition, and standard reading of all VFA. All the morphometric assessments were made by two experienced investigators after training sessions and after a previous global visualization. Before diagnosis of fracture, a non-osteoporotic origin was considered for each deformity. However, even history of trauma was inquired, we cannot exclude that some subjects did not report remote traumas. The main limitations lie in the cross-sectional nature of the study and in the procedures used to select subjects, who were all volunteers and ambulatory. The study population had a higher prevalence of osteoporosis and higher VF prevalence than what was reported earlier in the normal Moroccan population [14] which was probably due to a hazard effect.

This study confirmed that men with asymptomatic densitometric VFs have lower BMD than subjects without VFs. They have evidence of higher SHBG levels and hence lower free sex steroids as well as increased bone resorption. It confirmed also that BMD and CTx are the most important determinant of asymptomatic VFs, and that SHBG is an independent risk factor that must be taken into account. However, large scale longitudinal studies are needed to further evaluate the relationship between this parameter and incident fractures.

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