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ORIGINAL ARTICLE

PTH level but not 25 (OH) vitamin D level predicts bone loss rates in the elderly

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Abstract
Summary We assessed the impact of calciotropic hormones on bone loss in 195 elderly subjects. After a median follow up of 4 years, parathyroid hormone (PTH) correlated negatively with changes in bone mineral density (BMD) at all skeletal sites. After adjustment for potential predictors of bone loss in the elderly, PTH level alone explained 3% of the variance in BMD changes at the hip.
Introduction This study assessed the impact of calciotropic hormones on bone loss rates in an elderly population-based cohort of 195 ambulatory men and women, aged 65–85 years and followed up for a median of 4 years.
Methods Calcium intake, serum calcium, and phosphorus were assessed at baseline. Serum creatinine was measured at follow up visit. The 25 (OH) vitamin D [25-OHD] and PTH were measured at baseline and at follow up. Bone mass at the lumbar spine, hip, forearm and total body, as well as body composition was measured at baseline and at follow up by dual energy X-ray absorptiometry.
Results Mean 25-OHD level was 14.7±6.4 ng/ml and mean PTH level was 47.9±30.4 pg/ml. Age correlated negatively with percent changes in BMD at all skeletal sites ($p<0.05$). Changes in body mass index (BMI) and in body composition correlated positively with BMD changes at all sites, except at the forearm. There was no correlation between 25-OHD and changes in BMD except at the trochanter ($r=0.19$, $p<0.008$). Conversely, PTH negatively correlated with changes in BMD at all skeletal sites ($r=-0.14$ to -0.27, $p<0.05$). This correlation persisted after adjustment for age, changes in BMI, changes in fat mass and lean mass, serum creatinine, calcium intake, and 25-OHD levels. PTH level alone explained 3% of the variance in BMD changes at all hip subregions.
Conclusions Serum PTH, but not 25-OHD, predicted bone loss rates in the elderly. Thus, it is important to normalize PTH level when correcting hypovitaminosis D in the elderly.

Keywords Body composition · Bone loss · Elderly · PTH · Vitamin D

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Introduction

Osteoporosis is a substantial health problem in aging population in both genders. During lifetime, women lose 30–50% of their bone mass [1]. Bone loss starts before the menopause transition in females and accelerates during the first few years following menopause. Although men lose bone to a lesser extent than women, lifetime bone loss may reach 20% at cortical sites and 30% at trabecular sites [1]. Age-related bone loss has been primarily attributed to sex steroid deficiency. Indeed, estrogen has been shown to protect against bone loss in longitudinal studies [2]. However, a recent longitudinal study showed that, although endogenous free estradiol was associated with bone loss in postmenopausal women, only little amount (less than 1%) of the variance of bone loss was explained by this measurement [3], suggesting that other hormonal and/or non-hormonal factors play more important roles in bone

loss in these women. Indeed, bone loss in the elderly may be secondary to changes in calciotropic hormones, namely decreased vitamin D synthesis, and decreased calcium absorption, and increased parathyroid hormone (PTH) with aging.

Cross-sectional data showed a positive association between serum 25 (OH) vitamin D levels and bone mineral density (BMD) [4]. There is good evidence that older people with insufficient levels of vitamin D are at increased risk of osteoporosis and osteoporotic fractures [5]. On the other hand, high serum PTH levels have been associated with increased bone remodeling, excessive bone loss and increased fracture risk [6]. Vitamin D supplementation decreases serum PTH concentration, decreases bone turnover, increases bone mineral density, and decreases in fracture risk in the elderly [7].

Over the years, attention has been focusing on the role of vitamin D rather than PTH, although in some cross-sectional studies, PTH seems to be the mediator of the deleterious effect of hypovitaminosis D on bone [8, 9]. Indeed, we have shown that PTH levels, but not serum 25-OHD, were an independent predictor of BMD at all skeletal sites, after adjustment for predictors of bone mass in the elderly [8]. Similarly, Sahota et al. showed that patients with hypovitaminosis D and a blunted PTH response had higher BMD compared to those with hypovitaminosis D and elevated PTH levels [9]. Studies that prospectively evaluated the impact of calciotropic hormones on bone loss rates, namely the independent role of PTH, are scarce.

The current study aimed at assessing the relative impact of calciotropic hormones, on bone loss rates, in an elderly population-based cohort of Lebanese subjects.

Methods

Four hundred sixty elderly Lebanese (65–85 years) participated in a population-based study aiming at assessing the prevalence of osteoporosis and vertebral fractures in Lebanese elderly. Apparently healthy subjects were randomly selected from the Greater Beirut area using a multilevel cluster technique. Greater Beirut was broken down into regions and subregions with households. The households were chosen randomly from the maps and the subject/household who fits the age range was selected. The study subjects were recruited between November 2002 and March 2003. One hundred ninety-five subjects (65 men and 130 women) returned for follow up after a mean duration of 4.2±0.3 years. Three subjects were excluded from the analyses because of suspected primary hyperparathyroidism based on a calcium level ≥10 mg/dl and PTH above the upper limit of normal at baseline. Data pertaining to the 192 subjects who presented for follow up was used for the purpose of this study. Exclusion criteria were the following: any medical condition likely to affect bone metabolism such as the history of major chronic disease, the intake of medications that affect bone metabolism, history of steroid intake for more than 6 months, treatment with bisphosphonates, selective estrogen receptor modulators, calcitonin or hormone replacement therapy for more than 1 year during the previous 5 years, bed rest for more than 1 month within 6 months prior to the study, subjects with previous surgery on the spine or both hips, and those with history of radiotherapy or chemotherapy. Subjects with conditions technically interfering with dual-energy X-ray absorptiometry (DXA) BMD assessment were also excluded, i.e., previous surgery on the spine, hip, forearm, or an imaging contrast procedure within the past week.

Patient's height (centimeter) and weight (kilogram) were measured at baseline and at follow-up visit and BMI were calculated. Dairy calcium intake was assessed using a food frequency questionnaire that evaluated the consumption of calcium enriched food, stressing specifically dairy products usually consumed by the elderly of our population. This questionnaire was derived from a validated one developed in our unit that demonstrated that 80% of calcium intake in Lebanese adolescents was from dairy products [10]

Serum calcium (milligrams per deciliter), phosphorus (milligrams per deciliter), and alkaline phosphatase (international units per liter) were measured at baseline and at follow-up visits and serum creatinine (milligrams per deciliter) at follow up by standard calorimetric methods using the Hitachi 912 analyzer (Mannheim, Germany). Serum 25 (OH) vitamin D [25-OHD] in nanogram per milliliter was measured at baseline and at follow up with radioimmunoassay (IDS Immunodiagnostics, Boldon, UK). Serum PTH was measured by enzyme-linked immunosorbent assay-PTH immunoradiometric assay (CisBio International, Gif-Sur-Yvette, Cedex, France). The reference range reported in the kit is 8–76 pg/ml. At our lab, quality assurance is performed regularly and the intra-assay and inter-assay variability for 25-OHD and PTH are below 10%. The endocrine laboratory at our institution is a participant in the international vitamin D external quality assurance service, DEQAS (www.deqas.org).

BMD of the lumbar spine, the hip (total hip, femoral neck, and trochanter), and the forearm (33% radius), as well as total body bone mineral content (BMC) and body composition were measured at baseline by DXA in two centers using a Hologic 4500 A device (n=230) and a Hologic 4,500 W (n=230; Hologic, Bedford, MA, USA). Thirty subjects had BMD at all skeletal sites simultaneously measured in both centers. Linear regression analyses were

performed to allow conversion from one device (QDR W) to the other (QDR A) to derive cross-calibration formulas that were consistent with those reported in the literature [8]. Data therefore used were those as if as if all subjects were measured initially on the Hologic 4500 A densitometer using these cross-calibration formulas. At follow up, all patients had their BMDs measured at the American University of Beirut Medical Center using the same device (QDR-4500 A) and by the same BMD technician. At our center, same-day duplicate scans are performed for all skeletal sites on a daily basis and the mean±SD precision is calculated monthly. These values have been stable over years, similar to those reported in the literature, and well below the guidance cutoffs provided by the International Society of Clinical Densitometry. The mean CV±SD for duplicate skeletal measurements between 2002 and 2006 was below 0.9±0.8% at the lumbar spine and total hip, 1.5±1.3% at the femoral neck, 1.3±0.9% at the trochanter, and below 0.95±0.85% at the 1/3 radius.

The study was approved by the Institutional Review Board of the American University of Beirut. Written informed consent was obtained from the study participants.

Statistical analysis

Values are presented as mean±SD unless stated otherwise. *P* values of <0.05 were considered significant.

The mean values of 25-OHD and PTH levels [(baseline levels+follow-up levels)/2] were used in the analyses.

The study subjects were divided into subgroups according to three categories: 25-OHD >20 ng/ml, 25-OHD <20 ng/ml and normal PTH levels, and 25-OHD <20 ng/ml and high PTH levels. There were too few subjects ($N=5$) with 25-OHD levels of >30 ng/ml to use this cutoff value for analyses. One-way analysis of variance was performed to assess the difference in BMD changes between these three categories. Paired *t* test was used to assess the significance of changes in BMD from baseline, and independent *t* test was used to compare the mean of continuous variables between males and females. Pearson's correlations were used to assess the relationship between the percent changes in BMD and continuous variables such as age, changes in BMI, changes in body composition, serum calcium, calcium intake, serum 25-OHD level, and serum PTH levels. Partial correlations were then performed to assess the effect of PTH on BMD changes, after adjustment for each variable at a time. Linear regression models were then built to assess the effect of PTH on BMD changes, after adjusting for all variables of other covariates of interest including age, calcium intake, creatinine, 25-OHD, changes in fat mass, and changes in lean mass all entered in the same model.

Results

Characteristics of the study population

Baseline characteristics of the study population are shown in Table 1. The mean age in the overall group at study entry was 72.5±5.1 years. The mean 25-OHD was insufficient in the overall group and within both genders.

Vitamin D levels correlated negatively with PTH levels both at baseline ($r=-0.31$, $p<0.001$) and at follow up ($r=-0.20$, $p=0.01$). Similarly, mean vitamin D levels correlated negatively with mean PTH ($r=-0.25$, $p=0.001$).

Subjects who lost to follow up were older (mean age 74±5.0 years) and had a baseline forearm and hip BMD and T scores that were lower than those who came for follow up visit; but their 25-OHD and PTH levels were similar to those subjects who participated in the follow-up study.

BMD changes from baseline

In the overall group, BMD decreased at all skeletal sites compared to baseline ($p<0.001$) except at the spine (Table 2). The percent changes in BMD at a mean follow up of 4.2±0.3 years varied between −2.44±5.7% and −4.7±8.9%, depending on skeletal site. The corresponding annualized percent changes ranged from −0.58±1.3% to −1.11±2.1%. There was no significant difference in BMD changes between men and women except at the femoral neck where bone loss was more pronounced in women (−3.7% vs. −0.8, $p=0.02\%$).

Bivariate correlations between changes in BMD and potential predictors

There was a significant negative correlation between age at baseline and percent changes in bone density at the spine, total hip, trochanter, and forearm ($r=-0.15$ to -0.21, $p<0.05$) and with percent changes in total body BMC ($r=-0.19$, $p<0.01$; Table 3).

Changes in BMI positively correlated with percent changes in BMD at the spine ($r=0.32$, $p=0.001$), total hip ($r=0.36$, $p<0.001$), and femoral neck ($r=0.29$, $p<0.001$) but not at the trochanter and the forearm. Similarly, changes in fat mass and in lean mass positively correlated with percent changes in total body BMC and with changes in BMD at all sites except the forearm BMD ($r=0.26$–0.50, $p<0.01$).

There was no correlation between serum calcium or calcium intake and percent changes in bone mass at any skeletal site.

There was no significant correlation between bone loss rates and serum 25-OHD or PTH levels at baseline (data not shown). There was a mild correlation between mean

Table 1 Baseline characteristics of the study population

	Overall (n=192)	Men (n=64)	Women (n=128)
Age (years)	72.3±5.1	72.9±5.0	72.1±5.1
Height (cm)	155.5±8.4	163.6±6.6	151.4±5.9
Weight (kg)	71.7±14.3	73.0±11.9	71.1±15.4
BMI (kg/m^2)	29.7±6.0	27.2±3.7	31.0±6.5
Spine T-score	−2.2±1.3	−1.7±1.6	−2.3±1.2
Total hip T-score	−1.7±0.9	−1.5±1.0	−1.8±0.8
Femoral neck T-score	−2.6±0.8	−2.7±0.9	−2.6±0.7
Trochater T-score	−1.8±1.0	−1.5±1.0	−2.0±0.9
Forearm T-score	−2.6±1.3	−2.6±1.5	−2.6±1.2
Subtotal body T-score	0.84±0.1	0.9±0.09	0.7±0.08
BMD spine (g/cm^2)	0.838±0.15	0.918±0.16	0.799±0.13
BMD total hip (g/cm^2)	0.790±0.12	0.872±0.123	0.749±0.10
BMD femoral neck (g/cm^2)	0.647±0.08	0.681±0.09	0.630±0.07
BMD trochanter (g/cm^2)	0.566±0.10	0.629±0.11	0.535±0.08
BMD forearm (g/cm^2)	0.580±0.10	0.678±0.08	0.530±0.07
Subtotal body BMC (g)	1,366±338	1,689±303	1,203±216
Subtotal body fat mass (g)	24,257±8,403	18,064±5,676	27,379±7,815
Subtotal body lean mass (g)	40,699±7,325	47,303±6,679	37,370±5,028
Serum calcium (mg/dl)	9.4±0.5	9.2±0.4	9.5±0.5
Serum phosphorus (mg/dl)	3.4±0.5	3.1±0.4	3.6±0.5
Serum Alk Ph (IU/L)	85.0±30.8	76.6±21.6	89.4±33.9
Serum creatinine[a] (mg/dl)	0.8±0.3	1.0±0.4	0.8±0.3
Serum 25-OHD[b] (ng/ml)	14.7±6.4	14.7±4.0	14.6±7.4
Serum PTH[b] (pg/ml)	47.9±30.4	47.0±35.6	48.3±27.5
Estimated daily calcium intake (mg)	288±242	323±245	269±239
Smoking status			
Never	39.2%	24.2%	47.1%
Ex-smokers	28.2%	35.5%	24.4%
Current smoker	32.6%	40.3%	28.6%

[a] Serum creatinine was measured at follow up visit only

[b] Values of 25-OHD and PTH represent the average of two measurements obtained at baseline and at follow up

serum 25-OHD and percent changes in BMD at the trochanter site only (r=0.19, p<0.008). Mean serum PTH negatively correlated with percent changes in BMD at all skeletal sites (r=−0.14 to −0.27, p<0.05) in the overall group. The negative correlation between PTH and rates of bone loss was linear at all skeletal sites. Within genders, this negative relationship was present at the total hip and trochanter (r=−0.25 to −0.34, p<0.05) in men, and at the spine, femoral neck, trochanter, and forearm (r=−0.20 to −0.45, p<0.05) in women.

Adjusted analyses

Partial correlations

The rates of bone loss were significantly higher in subjects who had 25-OHD below 20 ng/ml and high PTH levels (n=22, mean±SD 25-OHD 10.1±2.7 ng/ml and mean± SD PTH 122±51 pg/ml), compared to those who had 25-OHD below 20 ng/ml with normal PTH levels (n=140, mean±SD 25-OHD 13.0±3.3 ng/ml and mean SD±PTH 41.4±13.9 pg/ml); p=0.03 at the spine, p=0.02 at the total hip, and p=0.03 at the trochanter; and to those who had 25-OHD levels ≥20 ng/ml (n=30, mean±SD 25-OHD 25.3±8.4 ng/ml, and mean±SD PTH 35.2±13.7 pg/ml); p=0.01 at the spine, p=0.03 at the total hip, and p=0.02 at the trochanter (Fig. 1).

The negative correlation between PTH and percent changes in BMD persisted at most skeletal sites after adjustment for each of the other predictors of bone loss entered at one time, such as age, changes in BMI, changes in fat mass, changes in lean mass, serum creatinine, calcium intake, and serum 25-OHD levels (Table 4).

Multivariate model

After adjustment for age, calcium intake, serum creatinine and 25-OHD in multivariate models, mean PTH level, and

Table 2 Total percent changes and annualized percent changes in bone mineral density in the overall study population and by genders

	Overall (n=192)	P value[a]	Men (n=64)	Women (n=128)	P value[b]
Unadjusted percent changes					
Lumbar spine BMD	0.73±9.7	NS	1.23±9.9	0.46±9.7	NS
Total hip BMD	−4.31±7.3	<0.001	−4.09±5.8	−4.42±8.0	NS
Femoral neck BMD	−2.73±8.3	<0.001	−0.78±7.7	−3.71±8.5	0.02
Trochanter BMD	−4.73±8.9	<0.001	−4.65±8.3	−4.77±9.1	NS
Forearm BMD	−2.44±5.7	<0.001	−2.74±5.4	−2.29±5.9	NS
Subtotal body BMC	−4.63±7.1	<0.001	−4.6±7.7	−4.6±5.7	NS
Subtotal body fat mass	−1.73±15.8	NS	−3.4±15.7	1.43±15.8	0.05
Subtotal body lean mass	−1.45±5.2	NS	−1.2±5.5	−1.80±4.6	NS
Annualized percent changes					
Lumbar spine BMD	0.18±2.3	NS	0.31±2.4	0.10±2.3	NS
Total hip BMD	−1.01±1.7	<0.001	−0.97±1.3	−1.03±1.9	NS
Femoral neck BMD	−0.64±2.0	<0.001	−0.19±1.9	−0.87±2.0	0.03
Trochanter BMD	−1.11±2.1	<0.001	−1.12±1.9	−1.11±2.2	NS
Forearm BMD	−0.58±1.3	<0.001	−0.65±1.3	−0.54±1.4	NS
Subtotal body BMC	−1.10±1.6	<0.001	−1.10±1.8	−1.12±1.3	NS
Subtotal body fat mass	−0.41±3.8	NS	−0.79±3.8	0.34±3.8	0.05
Subtotal Body Lean Mass	−0.33±1.2	NS	−0.28±1.3	−0.43±1.1	NS

[a] P values for difference compared to baseline by paired t test

[b] P values for difference between genders by independent t test

Table 3 Pearson's coefficients of correlations between the percent changes in BMC or BMD at different skeletal sites and known predictors of bone loss in the overall group and within genders

	Age	BMI changes	fat mass changes	lean mass changes	Serum calcium	Serum 25-OHD	Serum PTH	Calcium intake
Overall group (n=192)								
Spine BMD	−0.21*	0.32***	0.26**	0.34***	–	–	−0.27**	–
Total hip BMD	−0.15*	0.36***	0.46***	0.36***	–	–	−0.20**	–
F. neck BMD	–	0.29***	0.27***	0.26***	–	–	−0.16*	–
Trochanter BMD	−0.17*	–	0.46***	0.44***	–	0.19**	−0.20**	–
Forearm BMD	−0.15*	–	–	–	–	–	−0.14*	–
SubTBody BMC	−0.19*	0.36***	0.50***	0.34***	–	–	–	–
Men (n=64)								
Spine BMD	–	–	–	0.38**	–	–	–	–
Total hip BMD	−0.25*	0.27*	0.31*	0.40***	–	0.31*	−0.34**	–
F. Neck BMD	–	–	–	–	–	0.36**	−0.07	–
Trochanter BMD	–	–	0.30*	0.34**	–	0.26*	−0.25*	–
Forearm BMD	–	–	–	–	–	–	–	–
SubTBody BMC	–	0.27*	0.34***	–	–	–	–	–
Women (n=182)								
Spine BMD	−0.22*	0.39***	0.42***	0.34***	–	–	−0.35***	–
Total hip BMD	–	0.38***	0.52***	0.35***	–	–		–
F. Neck BMD	–	0.31***	0.30***	0.31***	–	–	−0.22*	–
Trochanter BMD	–	–	0.54***	0.48***	–	–	−0.45***	–
Forearm BMD	–	–	0.18*	–	–	–	−0.20*	–
SubTBody BMC	–	0.38 [c]	0.58[c]	0.39[c]	–	–		–

(–), not significant

*p<0.05, **p<0.01, ***p<0.001

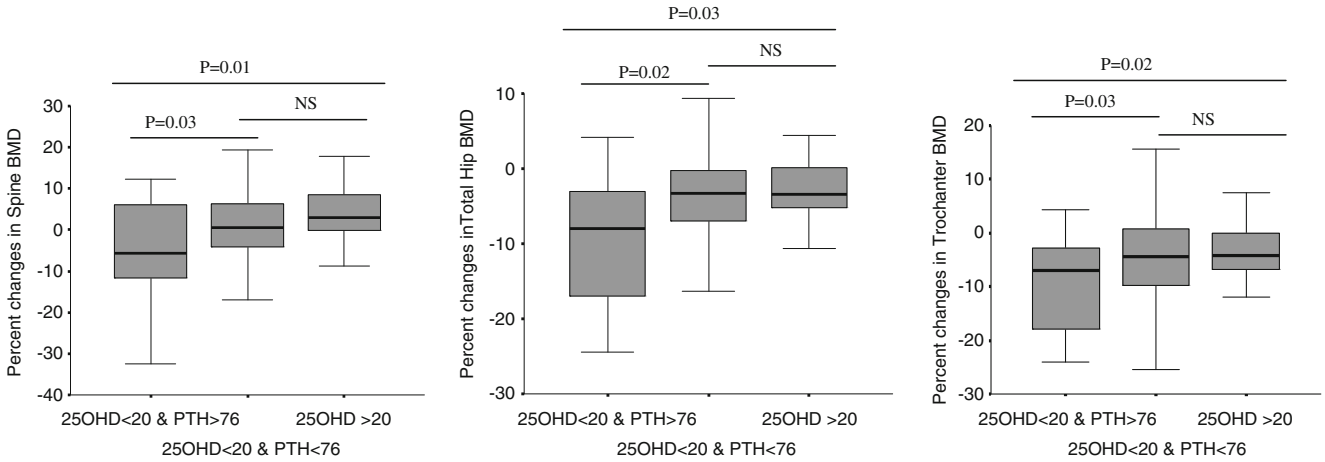

Fig. 1 *Box plot* showing the median, 25th and 75th percentile of the percent changes in BMD at the spine, total hip, and trochanter by PTH and 25-OHD levels in the overall group. There was no difference in bone loss rates between subjects with 25-OHD >20 ng/ml and those with low 25-OHD and normal PTH levels. Bone loss was significantly higher in subjects with low 25-OHD and high PTH levels compared to those with low 25-OHD and normal PTH levels

changes in fat mass and lean mass were independent predictors for percent changes in BMD at the total hip (R^2=27.9%), femoral neck (R^2=13.4%), and trochanter (R^2=31.7%). At all hip subregions, PTH alone explained 3% of the variance in BMD changes. The changes in lean mass and PTH were the only independent predictors of changes in BMD at the spine (R^2=23.7%), whereas changes in total body fat was the only independent predictor for changes in total body BMC (R^2=30.9%; Table 5).

Discussion

This longitudinal population-based study assessed the rate of bone loss in Lebanese elderly after a median follow up of 4 years. It showed that changes in body composition predicted bone loss in the elderly and that serum PTH level, but not serum 25-OHD, was an independent predictor of bone loss, after adjustment for other known predictors of bone mass changes in this age group.

Over the follow-up period, BMD decreased at all skeletal sites except at the spine. This difference between the spine and other skeletal sites may be related to the development of osteo-degenerative changes (ODC) at the spine that may falsely increase bone density measurements in elderly. The effect of degenerative changes on BMD was described in the early 1980s [11, 12]. The probability of developing degenerative changes increases from less than 10% before age of 50 years to 85% at age 70 years [12]. We had previously shown that ODC affected at least one vertebral BMD measurement in 70% of spine scans of elderly population [13]. The magnitude of BMD changes due to these ODC ranged between 4% and 14%, according to the severity of changes and to the vertebral level affected [12].

The rate of bone loss at the forearm and at the hip in our elderly population seems to be comparable to those reported by others. The annual rate of 0.6% at the forearm is well within the annual rates ranging between 0.4% and 1% reported at the forearm in Northern Norway [14] and in the Framingham longitudinal study [2]. Similarly, the annual rates of bone loss of 0.6% at the femoral neck and 1.0% at the total hip reported herein are comparable to the annual bone loss of 0.5% at the total hip and femoral neck reported in a study of elderly American women with mean age of 71.3 years [15].

There was a significant relationship between changes in BMI, in body composition, and changes in bone mass. The protective effect of obesity on bone mass has been well described in cross-sectional studies [16]. Also, positive correlations have been reported between bone density and both lean mass and fat mass [16, 17]. Dennison et al. showed that a lower BMI and a greater rate of loss of adiposity, but not vitamin D or PTH, predicted bone loss in elderly men and women aged 60–75 years followed up for 4 years [18]. In a 15-year follow-up study, Zhai et al. showed a protective role of increasing weight and lean mass on the long term bone loss in postmenopausal women [19]. Similarly, in a study assessing the effect of exercise-induced changes in body composition on BMD, in men aged 55–75 years, the change in lean mass was associated with total hip and femoral shaft BMD and the change in lean mass explained 9% of the variance in total hip BMD [20].

The rate of bone loss at the femoral neck was higher in women compared to men. This may be explained by the

Table 4 Partial correlations between PTH and percent changes in BMD at different skeletal sites, after adjustment for other predictors in the overall group

	Unadjusted	Adjusted for age	Adjusted for Δ BMI	Adjusted for creatinine	Adjusted for Δ fat mass	Adjusted for Δ lean mass	Adjusted for 25-OHD	Adjusted for calcium intake
Spine BMD	−0.27 (0.002)	−0.27 (0.002)	−0.26 (0.003)	−0.29 (0.001)	−0.30 (0.001)	–	−0.26 (0.003)	−0.28 (0.002)
Total hip BMD	−0.20 (0.005)	−0.20 (0.006)	−0.20 (0.005)	−0.21 (0.02)	−0.29 (0.001)	−0.21 (0.02)	−0.19 (0.008)	−0.23 (0.01)
F. Neck BDM	−0.16 (0.02)	−0.16 (0.02)	−0.15 (0.03)	−0.22 (0.01)	−0.22 (0.01)	−0.17 (0.06)	−0.14 (0.05)	−0.19 (0.03)
Trochanter BDM	−0.20 (0.004)	−0.20 (0.005)	−0.20 (0.004)	−0.25 (0.006)	−0.31 (<0.001)	−0.23 (0.01)	−0.19 (0.007)	−0.24 (0.008)
Forearm BDM	−0.14 (0.04)	−0.14 (0.05)	–	–	–	–	–	−0.11 (0.03)
SubTBody BMC	–	–	–	–	−0.19 (0.03)	–	–	–

(–), Not significant, Δ *BMI* changes in BMI, Δ *fat mass* changes in fat mass, Δ *lean mass* changes in lean mass

Table 5 Multivariate analyses showing the effect of PTH on percent changes in bone loss at different skeletal sites, after adjustment for all other predictors

		Age	Calcium intake	Creatinine	25-OHD	Δ Fat mass	Δ Lean mass	PTH	R^2 (%)
Spine BMD	β (SE)	−0.24 (0.16)	−0.02 (0.004)	3.2 (1.9)	−0.007 (0.1)	0.09 (0.05)	0.4 (0.17)	−0.09 (0.02)	23.7
	p	0.1	0.4	0.09	0.9	0.1	0.02	0.001	
Total Hip BMD	β (SE)	−0.007 (0.09)	0.0005 (0.002)	0.14 (0.12)	−0.05 (0.08)	0.18 (0.03)	0.23 (0.10)	−0.04 (0.01)	27.9
	p	0.9	0.8	0.9	0.5	<0.001	0.02	0.009	
Femoral neck	β (SE)	0.09 (0.12)	0.0008 (0.003)	2.5 (1.6)	0.02 (0.09)	0.11 (0.04)	0.25 (0.13)	−0.05 (0.02)	13.4
	p	0.4	0.7	0.1	0.8	0.009	0.05	0.02	
Trochanter BMD	β (SE)	−0.09 (0.11)	0.008 (0.002)	1.11 (1.15)	−0.07 (0.09)	0.20 (0.04)	0.44 (0.12)	−0.06 (0.02)	31.7
	p	0.9	0.7	0.4	0.4	<0.001	<0.001	0.006	
Forearm BMD	β (SE)	−0.18 (0.08)	−0.007 (0.002)	0.31 (1.1)	0.05 (0.07)	0.005 (0.03)	0.003 (0.09)	−0.02 (0.01)	5.1
	p	0.04	0.6	0.7	0.4	0.8	0.6	0.2	
Subtotal body BMC	β (SE)	−0.07 (0.09)	0.003 (0.002)	0.07 (0.07)	−0.05 (0.07)	0.20 (0.03)	0.16 (0.09)	−0.02 (0.01)	30.9
	p	0.4	0.07	0.9	0.4	<0.001	0.09	0.2	

The models were built with percent changes in BMD of a skeletal site as outcome, and age, calcium intake, creatinine, 25-OHD, changes in fat mass and changes in lean mass and PTH as predictors, all entered in the same model. One model was built for each skeletal site separately

Δ *fat mass* changes in fat mass, Δ *lean mass* changes in lean mass

small sample size in men (n=64), but may also be attributed to the lower vitamin D and higher PTH levels in women. Indeed, the rate of bone loss has been associated with ethnicity, environmental factors, and vitamin D levels. In a longitudinal study in elderly Belgian men aged over 70 years and followed up for a median of 4 years [21], the rates of bone loss were lower than those found in our study (0.39% at the total hip and 0.04% at the femoral neck versus 0.5% at both regions in the current study). The mean 25-OHD was higher in the Belgian population compared to ours (23.4 versus 14.3 ng/ml), and may partially explain this difference in the rate of bone loss. However, there was no significant relationship between serum 25-OHD levels and rate of BMD loss at any skeletal site in the current study, except for a mild association at the trochanter. Cross-sectional studies showed an association between BMD and vitamin D levels in the elderly [4, 22, 23], whereas prospective studies lead to conflicting results. Garnero et al. showed that vitamin D status was not an important determinant of rate of bone loss at the forearm in postmenopausal women with mean age of 62.2 years followed prospectively for a median of 11.2 years [24]. Similarly, the Framingham Osteoporosis Study showed no association between serum 25-OHD level and the 4-year BMD loss in men and women with mean age of 74 years [2]. Another prospective population-based study including elderly men and women aged between 60 and 75 years, showed no association between serum 25-OHD level and rate of bone loss at the hip or spine [18]. Conversely, in the study of osteoporotic fractures, serum 25-OHD levels were associated with the rate of bone loss in elderly women at the hip but not at the calcaneus, after a follow up of 3.4 and 5.7 years, respectively [15]. Moreover, it has been shown that serum 25-OHD concentration above 50 nmol/l leads to further reduction in bone loss at the spine and hip in patients on antiresorptive therapy [25, 26]. In a longitudinal follow up from the Osteoporotic Fractures in Men Study, after a median follow up of 4.4 years, the annual rate of bone loss at the hip ranged between −0.37% and −0.59%. The rate differed according to vitamin D level and the age of the population [27]. Lower levels of 25-OHD were associated with higher rates of bone loss at the hip in men older than 75 years, whereas there was no evidence of an association between 25-OHD level and rate of hip bone loss among younger men [27]. Whether 25-OHD level was associated with rate of bone loss in the oldest subjects in our population could not be assessed in the current study in view of the small sample size.

In contrast, and contrary to 25-OHD levels, PTH levels in our study inversely correlated with the rate of bone loss at all skeletal sites in a consistent pattern. The strength of this relationship did not change after adjustment for other predictors of bone loss in the elderly such as age, changes in body composition, creatinine, or vitamin D level. Moreover, there was no significant difference in the rate of bone loss between subjects who had low 25-OHD levels with normal PTH and those who had 25-OHD levels above 20 ng/ml, whereas the rate of bone loss was higher in subjects who had high PTH levels compared to the two other groups. The above findings suggest that PTH levels, rather than serum 25-OHD, predict rates of bone loss in the elderly. The difference between groups seen at the total hip and trochanter were not significant at the femoral neck. The reason behind the lack of significance at the femoral neck, is unclear, however, it may be explained by the lower rate of bone turnover at the femoral neck, compared to the other two hip regions.

The effect of PTH on bone mass had been studied in cross-sectional studies. We have previously shown in a cohort of 460 elderly subjects with hypovitaminosis D that after adjustment for predictors of bone mass in the elderly, PTH levels, but not serum 25-OHD, had significant independent contributions to BMD variance at all skeletal sites [8]. Sahota et al. showed that patients with hypovitaminosis D and a blunted PTH response were characterized by a reduced bone turnover and higher bone density as compared to those with hypovitaminosis D and secondary hyperparathyroidism [9]. Longitudinal data assessing the role of PTH in bone loss are scarce. Some [15, 18, 24] but not all studies [2, 27] that evaluated the relationship between 25-OHD and bone loss also evaluated the relationship with PTH. The OFELY study [24], the study of osteoporotic fractures [15] and the study by Dennison et al. [18] showed no relationship between the rate of bone loss and PTH level [15, 18, 24]. Conversely, a study assessing the age-related decline in femoral neck BMD in 82 men aged 25–86 years showed that, taking into account anthropometric and other biological factors possibly involved in bone aging, the effect of age on bone mass was largely explained by the age-related increase of PTH and decrease of IGF-1 [28]. In a study of 112 postmenopausal women who have been on bisphosphonates for a median of 3.8 years, BMD response at the hip site was impaired in patients who had a PTH level of >41 ng/l [25].

In a meta-analysis of five large randomized placebo controlled trials, vitamin D supplementation reduced the risk of falls by more than 20% in older individuals [29]. Vitamin D supplementation was also associated with a decrease in risk of hip and any non-vertebral fractures by 25% [7]. A more recent meta-analysis by Boonen et al., an extension to the one above showed that oral vitamin D appeared to reduce the risk of hip (and any non-vertebral) fractures only when calcium was added [30]. Whether this

effect was related to more PTH suppression when calcium was added has not been addressed.

The current study has several strengths including the population-based and prospective design, the relatively long-term follow up, the repeated measurements of calciotropic hormones at baseline and at follow up, and the adjustment for strong predictors of bone loss such as age, body composition calcium intake, and kidney function. The study limitations include the relative small sample size by gender subgroups, and the lack of measurements of sex steroid hormones, powerful determinants of bone loss [15, 21, 31, 32] and fracture risk [33] in the elderly. Studies showed that bioavailable sex steroids explained between 0.6% and 5% of changes in bone density in elderly men and women [3, 34]. Pottelberg et al. showed that, after adjustment for age, fat mass, grip strength, and PTH, bioavailable estradiol was an independent predictor of changes in bone mass at the forearm, total hip, and femoral neck in men aged 70 years or older, whereas a negative PTH effect persisted only at the forearm [21]. In the current study, PTH alone explained 3% of changes in bone mass at the hip, a substantial proportion, considering comparable data on estradiol. Further studies are needed to evaluate the role of PTH on bone loss, after adjustment for sex steroid hormones. The low mean vitamin D levels of the recruited population may affect the results. It is likely that the association between bone loss and serum vitamin D levels may not be observed when vitamin D levels are very low. Therefore, although the findings of the current study are relevant to other populations in the Middle East with similarly low vitamin D levels, they may not be valid for subjects from regions with more replete levels. Finally, it is possible that the high rate of loss to follow up may have affected the results. Indeed, subjects who lost to follow up were older and had lower BMD values at baseline.

In conclusion, this study showed that, after a median follow up of 4 years, the annualized rates of bone loss in elderly Lebanese population are similar to those reported by others. Changes in body composition, and serum PTH levels, but not 25-OHD levels predicted rates of bone loss at the hip and forearm in elderly men and women with low serum vitamin D levels. Aiming at normalizing PTH, as opposed to targeting specific D levels, may be the best approach to optimize skeletal health in elderly with low vitamin D levels.

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Conflicts of interests None

References

1. Riggs BL, Melton LJ 3rd (1986) Involutional osteoporosis. N Engl J Med 314:1676–1686
2. Hannan M, Felson D, Dawson-Hughes B (2000) Risk factors for longitudinal bone loss in elderly men and women: the Framingham Osteoporosis Study. J Bone Miner Res 15:710–720
3. Bjørnerem A, Emaus N, Berntsen GK et al (2007) Circulating sex steroids, sex hormone-binding globulin, and longitudinal changes in forearm bone mineral density in postmenopausal women and men: the Tromsø study. Calcif Tissue Int 81:65–72
4. Bischoff-Ferrari HA, Dietrich T, Orav J, Dawson-Hughes B (2004) Positive association between 25-hydroxyvitamin D levels and bone mineral density: a population-based study of younger and older adults. Am J Med 116:634–639
5. Van Schoor NM, Visser M, Pluijm SM, Kushuk N, Smit JH, Lips P (2008) Vitamin D deficiency as a risk factor for osteoporotic fractures. Bone 42:260–266
6. Mosekilde L (2008) Primary hyperparathyroidism and the skeleton. Clin Endocrinol Oxf 69:1–19
7. Bischoff-Ferrari HA, Willett WC, Wong JB, Giovannucci E, Dietrich T, Dawson-Hughes B (2004) Fracture prevention with vitamin D supplementation: a meta-analysis of randomized controlled trials. JAMA 291:1999–2006
8. Arabi A, Baddoura R, Awada H et al (2006) Hypovitaminosis D osteopathy: is it mediated through PTH, lean mass, or is it a direct effect? Bone 39:268–275
9. Sahota O, Mundey MK, San P et al (2004) The relationship between vitamin D and parathyroid hormone: calcium homeostasis, bone turnover, and bone mineral density in postmenopausal women with established osteoporosis. Bone 35:312–319
10. Salamoun M, Kizirian A, Tannous R et al (2005) Low calcium and vitamin D intake in healthy children and adolescents and their correlates. Eur J Clin Nutr 59:177–184
11. Krolner B, Berthelsen B, Nielson SP (1982) Assessment of vertebral osteopenia. Comparison spinal radiography and dual-photon absorptiometry. Acta Radiol Diagn 23:517–521
12. Rand T, Seidl G, Kainberger F et al (1997) Impact of spinal degenerative changes on the evaluation of bone mineral density with DXA. Calcif Tissue Int 35:667
13. Baddoura R, Arabi A, Haddad-Zebouni S (2007) Vertebral fracture risk and impact of database selection on identifying elderly Lebanese with osteoporosis. Bone 40:1066–1072
14. Emaus N, Berntsen G, Joakimsen R, Fonnebø (2006) Longitudinal changes in forearm bone mineral density in women and men aged 45–84 years: The Tromsø study, a population based study. Am J Epidemiol 163:441–449
15. Stone K, Bauer D, Black D, Sklarpin P, Ensrud K, Cummings S, for the Study of Osteoporotic Fractures Research Group (1998) Hormonal predictors of bone loss in elderly women: a prospective study. J Bone Miner Res 13:1167–1174
16. Reid IR (2008) The relationships between fat and bone. Osteoporos Int 19:595–606
17. Ho-Pham LT, Nguyen ND, Lai TQ, Nguyen TV (2010) Contributions of lean mass and fat mass to bone mineral density: a study in postmenopausal women. BMC Musculoskelet Disord 26:59
18. Dennison E, Eastell R, Fall CH et al (1999) Determinants of bone loss in elderly men and women: a prospective population-based study. Osteoporos Int 10:384–391
19. Zhai G, Hart DM, Valdes AM, Spector et al (2008) Natural history and risk factors for bone loss in postmenopausal Caucasian

women: a 15-year follow-up population-based study. Osteoporos Int 19:1211–1217
20. Stewart KJ, Bacher AC, Hees PS et al (2005) Exercise effects on bone mineral density relationships to changes in fitness and fatness. Am J Prev Med 28:453–460
21. Pottelbergh V, Goemaere S, Kaufman J (2003) Bioavailable estradiol and an aromatase gene polymorphism are determinants of bone mineral density changes in men over 70 years of age. J Clin Endocrinol Metab 88:075–3081
22. Collins D, Jasani C, Fogelman I, Swaminathan R (1998) Vitamin D and bone mineral density. Osteoporos Int 8:110–114
23. Fradinger E, Zanchetta J (2001) Vitamin D and bone mineral density in ambulatory women living in Buenos Aires, Argentina. Osteoporos Int 12:24–27
24. Garnero P, Munoz F, Sornay-Rendu E, Delmas PD (2007) Associations of vitamin D status with bone mineral density, bone turnover, bone loss and fracture risk in healthy postmenopausal women: The OFELY study. Bone 40:716–722
25. Deane A, Constancio L, Fogelman I, Hampson G (2007) The impact of vitamin D status on changes in bone mineral density during treatment with bisphosphonates and after discontinuation-following long-term use in post-menopausal osteoporosis. BMC Musculoskelet Disord 8:3. doi:10.1186/1471-2474-8-3
26. Adami S, Giannini S, Bianchi D, Sinigaglia L, Di Munno O, Fiore C, Minisola S, Rossini M et al (2009) Vitamin D status and response to treatment in post-menopausal osteoporosis. Osteoporos Int 20:239–244
27. Ensrud K, Taylor B, Paudel M, for the Osteoporotic Fractures in Men (MrOS) Study Group et al (2009) Serum 25-hydroxyvitamin D levels and rate of hip bone loss in older men. J Cl Endocrinol Metab 94:2773–2780
28. Blain H, Vuillemin A, Blain A et al (2004) Age-related femoral bone loss in men: evidence for hyperparathyroidism and insulin-like growth factor-1 deficiency. J Gerontol A Biol Sci Med Sci 59:1285–1289
29. Bischoff-Ferrari HA, Dawson Hughes B, Willett WC, Staehelin HB, Bazemore MG, Zee RY, Wong JB (2005) Effect of vitamin D on falls: a meta-analysis. JAMA 293:2257–2264
30. Boonen S, Lips P, Bouillon R, Bischoff-Ferrari HA, Vanderschueren D, Haentjens P (2007) Need for additional calcium to reduce the risk of hip fracture with vitamin d supplementation: evidence from a comparative meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 92:1415–1423
31. Gennari L, Merloti D, Martini G et al (2003) Longitudinal association between sex hormone levels, bone loss, and bone turnover in elderly men. J Clin Endocrinol Metab 88:5327–5333
32. Kuchuk NO, van Schoort NM, Pluijm S, Smith JH, de Ronde W, Lips P (2007) The association of sex hormone levels with quantitative ultrasound, bone mineral density, bone turnover and osteoporotic fractures in older men and women. Clin Endocrinol 67:295–303
33. Mellström D, Vandenput L, Mallmin H et al (2008) Older men with low estradiol and high serum SHBG have an increased risk of fractures. J Bone Miner Res 23:1548–1551
34. Yoshimura N, Muraki S, Oka H, Kawaguchi H, Nakamura K, Akune T (2011) Capacity of endogenous sex steroids tp predict bone loss in Japanese men: 10-year follow up of the Taiji cohort study. J Bone Miner Metab 29(1):96–102