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Seasonal changes in biochemical markers of bone metabolism and hip bone mineral status in older northern Chinese men and women

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Abstract: Objective To evaluate whether bone metabolism and bone mineral status of this population differs by season. **Methods:** 30 men and 29 women aged 60 ~ 75 years from Shenyang, northern China were studied longitudinally in March (spring) and September (autumn). Fasting plasma and urine were analysed for calcium, phosphate, PTH, 25(OH) D, 1,25$(OH)_2$D, osteocalcin and free deoxypyridinoline (DPD). Hip bone mineral status was measured using Lunar DXA (DPX-L, GE Lunar, Madison, US). **Results** Compared with spring, 25 (OH) D, calcium (albumin adjusted) and phosphate were higher in autumn whilst PTH was lower in both men and women. In addition, 1,25$(OH)_2$D concentration was higher in men ($P < 0.05$) but not in women and DPD/Creatinine was lower in women but not in men, compared with spring. Femoral neck BMC and total hip BMD in autumn were 2.5% (SE1.1) and 1% (SE0.4) higher in women ($P < 0.05$). An increase in total hip BMD [0.9% (SE0.5)] was also seen in men but not significant. No significant seasonal change was found with other markers in the studied and bone sites. **Conclusion** Seasonal changes in vitamin D status and Plasma PTH concentration are associated with seasonal changes in some markers of bone metabolism and bone mineral status at hip in an older northern Chinese population.

Key words: Bone metabolism; Bone mineral status; Season

中国北方老年人骨代谢生化指标和髋部骨矿状态的季节变化

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摘要:目的 为了解北方老年人骨矿状态和骨代谢是否存在季节变化。**方法** 沈阳市 60 ~ 75 岁老年人 59 人,其中男性 30 人,女性 29 人。于 3 月份(春季)和 9 月份(季秋)分别采集清晨空腹静脉血和尿,分析血浆中钙、磷、甲状旁腺激素、25(OH)D、1,25$(OH)_2$D、骨钙素;尿中钙、磷、脱氧吡啶啉(DPD)。用 DPX-L 双能 X 线吸收仪(Lunar, USA)测定研究对象髋部骨密度和骨矿含量。**结果** 男女血浆 25(OH)D、钙(经血浆蛋白调整)和磷含量秋季均高于春季,而甲状旁腺激素含量秋季低于春季。男性血浆 1,25$(OH)_2$D 含量秋季高于春季($P < 0.05$)。女性尿中 DPD/肌酐比值秋季低于春季($P < 0.05$)。女性股骨径骨矿含量和全髋部骨密度秋季比春季分别高 2.5%和 1%($P < 0.05$)。在男性全髋部骨密度秋季比春季高 0.9%,但差异没有统计学意义。其它指标没有观察到季节变化。**结论** 中国北方老年人维生素 D 营养状态、骨代谢和髋部骨矿状态存在季节变化。

关键词:骨代谢;骨矿状态;季节

1 Introduction

Low vitamin D status and associated rise in parathyroid hormone (PTH) in circulation were implicated in the pathogenesis of bone loss in the elderly[1,2]. Many studies examined seasonal fluctuations in vitamin D-PTH axis[3,4]. However, only few studies investigated the effect of season on bone metabolism or bone mineral status within the same individuals longitudinally and the results were inconsistent. Three longitudinal studies conducted in healthy Caucasian men and women of different age demonstrate significant seasonal variations in biochemical markers of bone turnover with typically bone resorption markers increasing in spring and decreasing in autumn periods[5-7] whilst seasonal variations have not been observed by others[8-11]. Evidence for significant seasonal changes in bone mineral density (BMD) or bone mineral content (BMC) has also been reported in healthy men, pre- and postmenopausal women, as well as in more elderly women[12-15]. Other researchers did not found seasonal variation in bone mineral status in their studies[9,11,16,17].

The effect of season on bone turnover and metabolism could be determined by geographical location or by the characteristics of the population studied. Our previous cross-sectional studies demonstrate that vitamin D status in spring in older people from Shenyang, northern China was very low with a mean plasma 25(OH)D concentration of 29 nmol·L^{-1}, meanwhile PTH concentration was higher compared with their British counterparts[18,19]. The aim of this study was to evaluate longitudinally whether bone metabolism and bone mineral status of a group of older individuals from Shenyang differs by season.

2 Subjects and methods

2.1 Subjects

Shenyang, which latitude is 42° N, is one of the largest cities in the northeast of the People's Republic China. There is a long and cold winter in this region (from November to early March). The temperature in December and January is usually between −15℃ to −30℃. There is also a hot and shining summer. The temperature during July and August is usually between 25℃-35℃.

30 men and 29 women aged 60-75 years were studied in March and September in 2000. This group of subjects was a subset of volunteers participated in a study investigating vitamin D and K status and bone health in older Chinese and British adults conducted collaboratively by MRC Human Nutrition Research, Cambridge, UK and Shenyang Medical College, Shenyang[19,20]. Exclusion criteria of the study were pathological disorders of medications known to alter calcium and bone metabolism. Ethical approval was given by the Academic Committee of Shenyang Medical College. All participants provided informed written consent.

2.2 Assessments of biochemical markers, bone mineral status and others

In both seasons, blood samples were collected between 7:00 AM and 9:00 AM after an overnight fasting. Two-hour fasting urine samples (after first void in the morning) were also collected. Plasma was separated from blood cells by a refrigerated centrifugation and stored at −80℃ until analysis.

Plasma calcium, phosphate, albumin, creatinine and urinary calcium, phosphate, creatinine concentrations were measured by colorimetric methods (Thermo Clinical Labsystems Oy, Espoo, Finland). Plasma creatinine was used as an indicator of renal function. The intra-and inter-assay coefficient variation (CV) of the above markers were all less than 5%. Plasma calcium was adjusted for albumin using an equation derived from the albumin-calcium relationship in this population: if albumin > 36g·L^{-1}, pCa − 0.01356 * [albumin − 36.0] and if albumin < 36g·L^{-1}, pCa + 0.01356 * [36.0-albumin]. Urinary concentrations of calcium and phosphate were expressed relatively to urinary creatinine (Cr) concentration.

Plasma 25 (OHD) was measured by radioimmunoassay (DiaSorin, Stillwater, MN, USA). The intra- and inter-assay coefficients of variation (CVs) were 10% and 11%, respectively. Plasma intact PTH 1-84 was measured by an immunoradiometric assay (DiaSorin, Stillwater, MN, USA). The intra- and inter-assay CVs were 4% and 14%, respectively. Plasma 1, 25-dihydroxyvitamin D (1,25$(OH)_2$D) was analyzed by radioimmunoassay (IDS, Boldon, Tyne and Wear, UK). The intra- and inter-assay CVs were 4.7% and 5.0%

respectively. Urinary free deoxypyridinoline (DPD) was analyzed using a competitive enzyme immunoassay (Metra Quidel Corporation, San Diego, CA, USA). The intra- and inter-assay CVs were 4.2% and 13.3%, respectively. DPD concentration was expressed relatively to urinary creatinine concentration. Plasma osteocalcin was analysed by one-step ELISA (Nordic Bioscience Diagnostics A/S, Herlev, Denmark). This assay measured intact osteocalcin and the large N-terminal-mid molecule fragment. The intra- and inter-assay CV were 4.1% and 10.5% respectively.

Bone mineral content (BMC), bone mineral density (BMD), and bone area (BA) at the left hip were measured in both seasons using dual-energy X-ray absorptiometry (DPX-L, GE Lunar, Madison, US). On the day the bone scan was given, calcium intakes of the subjects were assessed by a food questionnaire. Information about current use of vitamin D and calcium supplements was also collected.

2.3 Statistical analysis

Statistical analysis was performed by Linear Model software in Data desk 6.1.1 (Data Descriptions, Ithaca, NY, USA). To correct for skewed distributions and to permit exploration of proportional relationships, all continuous variables except age were converted to natural logarithms. In natural logarithms, group differences × 100 correspond closely to percent differences calculated as (difference/mean) × 100[21]. The seasonal differences (percent differences) in Table 1 and 2 were all obtained in this manner.

The percent change in biochemical markers and bone mineral measurements from spring to autumn for each gender group were determined by ANOVA models followed by Sheffé post-hoc tests with subject ID and season as dependent variables. The effect of gender on the rate of change was performed with two gender data pooled together by hierarchical ANOVA models where gender nested by subject ID was included as a dependent variable. Regression analysis was performed to examine possible predictors of seasonal change using both dependent and independent variables expressed as percent change from spring to autumn (Ln value autumn-Ln value spring). Interaction term was introduced to consider the effect of gender. All statistical models were set up in the same way, i. e. full models were generated and then variables $P > 0.05$ were removed by backward elimination to provide a parsimonious model.

3 Results

On average, men were 3 years older than women (Table 1). Eight men and 13 women reported calcium or vitamin D usage at the time of the study. Significant gender difference was found for most of the biochemical markers measured (Table 1). For example, plasma calcium, phosphate and osteocalcin concentrations; urinary calcium/Cr, phosphate/Cr and DPD/ Cr were higher in women that in men either in both seasons or in one of the seasons.

3.1 Seasonal changes

Mean concentrations of biochemical markers obtained in spring and autumn were summarised in Table 1. Compared with spring, plasma 25(OH)D concentration in autumn was increased significantly in both men (by 75%) and women (by 50%). With a smaller magnitude compared with 25(OH)D, 1,25$(OH)_2$D concentration in autumn was also increased in men but not in women (gender-season interaction, $P = 0.003$). Both plasma calcium and phosphate concentrations in autumn were significantly higher in women. To a lesser extent, the two markers were also increased in men though the increase for phosphate was not statistically significant (Table 1). Plasma PTH concentration was decreased in autumn than that in spring in both men ($P = 0.0001$) and women ($P = 0.0003$). DPD/Cr in autumn was decreased in women (by 50%) but no decrease was seen in men (gender-season interaction, $P = 0.0006$). No change was found with other biochemical markers. The inclusion of calcium and vitamin D usage in the analyses above did not have significant effects on the results.

Compared with spring, femoral neck BMC and total hip BMD in autumn were higher in women ($P = 0.03$ for both sites) (Table 2). An increase in total hip BMD was also observed in men ($P = 0.07$). No seasonal change was found for other bone measurements. Calcium and vitamin D use had no effects on the results.

Table 1 Subject characteristics and seasonal variations in biochemical markers of bone metabolism in older Chinese men and women

Item	Men ($n = 31$)			Women ($n = 29$)		
	Spring	Autumn	Δ% (SE) Autumn vs. Spring	Spring	Autumn	Δ% (SE) Autumn vs. Spring
Age (years)	67.4 (3.7)	68.2 (3.8)	—	64.1 (3.8)**	64.7 (4.0)**	—
Height (cm)	165.9 (6.0)	166.1 (6.0)	0.1 (0.1)	154.2 (5.6)**	154.3 (5.7)	0.1 (0.1)
Weight (kg)	66.8 (9.0)	66.3 (8.4)	−0.7 (0.6)	59.4 (11.7)**	58.9 (10.8)**	−0.6 (0.4)
Calcium intake ($mg \cdot d^{-1}$)	622 (284)	594 (238)	−3.5 (6.3)	627 (287)	533 (200)	−11.4 (9.7)
Plasma markers Albumin ($g \cdot L^{-1}$)	40.7 (3.0)	40.4 (3.4)	−1.0 (1.0)	40.6 (3.4)	42.0 (2.7)*	3.5 (1.1)
Total calcium ($mmol \cdot L^{-1}$)	2.12 (0.10)	2.20 (0.07)	3.6 (0.7)##	2.16 (0.12)	2.30 (0.07)**	6.5 (1.2)##
Phosphate ($mmol \cdot L^{-1}$)	0.84 (0.13)	0.87 (0.11)	3.1 (2.4)	1.04 (0.12)**	1.12 (0.13)**	7.4 (2.4)#
Creatinine ($\mu mol \cdot L^{-1}$)	84.1 (13.2)	81.4 (11.8)	−3.1 (2.3)	64.5 (10.8)**	71.3 (9.7)**	10.5 (3.0)##
PTH ($ng \cdot L^{-1}$)	32.5 (12.4)	22.7 (10.3)	−38.8 (6.5)##	31.0 (10.6)	24.2 (7.7)	−22.8 (7.2)#
25(OH)D ($nmol \cdot L^{-1}$)	23.5 (11.4)	45.3 (8.4)	74.7 (7.3)##	24.0 (9.5)	38.5 (9.8)**	49.9 (7.4)##
$1,25(OH)_2D$ ($pmol \cdot L^{-1}$)	97.2 (24.2)	118.4 (22.9)	20.1 (4.6)##	109.6 (29.2)*	111.6 (35.6)	−0.5 (4.8)
Osteocalcin ($\mu g \cdot L^{-1}$)	15.1 (8.7)	14.9 (8.5)	−3.1 (4.1)	19.1 (6.5)**	18.0 (8.2)*	−8.1 (4.6)
Urine markers Calcium/Creatinine (mmol/mmol)	0.43 (0.14)	0.52 (0.24)	14.2 (11.1)	0.68 (0.39)**	0.69 (0.25)**	8.5 (6.6)
Phosphate/Creatinine (mmol/mmol)	1.88 (0.45)	1.99 (0.92)	−0.3 (8.6)	2.47 (0.93)*	2.20 (0.88)	−12.6 (10.7)
DPD/Creatinine (nmol/mmol)	3.73 (1.52)	4.28 (1.80)	12.8 (10.5)	7.86 (3.60)**	5.37 (3.34)	−50.0 (13.7)##

Note: Data are provided as means (SD) unless otherwise noted. Differences were examined by Scheffé post hoc tests following analysis of covariance.

* $P < 0.05$, ** $P < 0.01$ women vs. men in the same season. # $P < 0.05$, ## $P < 0.01$ Autumn vs. Spring.

Table 2 Hip bone mineral status measured in Spring and Autumn in older Chinese men and women

Item	Men($n = 31$)			Women ($n = 29$)		
	Spring	Autumn	Δ% (SE) Autumn vs. Spring	Spring	Autumn	Δ% (SE) Autumn vs. Spring
Femoral neck BMC (g)	4.18 (0.70)	4.19 (0.69)	0.2 (0.7)	3.32 (0.47)**	3.40 (0.50)**	2.5 (1.1)#
Femoral neck BA (cm^2)	5.09 (0.28)	5.11 (0.29)	0.4 (0.5)	4.45 (0.48)**	4.51 (0.52)**	1.3 (0.9)
Femoral neck BMD (g/cm^2)	0.824 (0.121)	0.820 (0.122)	−0.5 (0.6)	0.748 (0.092)*	0.757 (0.095)*	1.2 (0.7)
Femoral trochanter BMC (g)	9.71 (2.36)	9.71 (2.52)	−0.4 (1.5)	7.00 (2.19)**	6.95 (2.23)**	−1.0 (2.3)
Femoral trochanter BA (cm^2)	13.1 (1.7)	13.0 (1.8)	−0.5 (1.1)	10.9 (2.0)**	10.7 (2.2)**	−2.0 (2.2)
Femoral trochanter BMD (g/cm^2)	0.735 (0.107)	0.736 (0.108)	0.2 (0.7)	0.634 (0.119)**	0.639 (0.115)**	1.0 (0.6)
Total hip BMC (g)	30.5 (5.5)	30.7 (5.5)	0.7 (0.7)	23.5 (4.4)**	23.5 (4.5)**	0.2 (0.6)
Total hip BA (cm^2)	33.9 (1.9)	33.9 (2.0)	−0.2 (0.4)	29.2 (2.6)**	28.9 (2.6)**	−0.7 (0.6)
Total hip BMD (g/cm^2)	0.894 (0.126)	0.901 (0.124)	0.9 (0.5)	0.803 (0.118)**	0.811 (0.118)**	1.0 (0.4)#

Note: Data are provided as means (SD) unless otherwise noted. Differences were examined by Scheffe post hoc tests following analysis of covariance.

* $P < 0.05$, ** $P < 0.01$ women vs. men in the same season.

3.2 Predictors of seasonal changes

There was a negative association between 25(OH)D concentration in spring and the percent increase in 25(OH)D in autumn [coefficient −0.78 (SE0.06), $P < 0.0001$], suggesting that subjects with a lower 25(OH)D concentration in spring had a larger increase in autumn. The percent decrease in plasma PTH concentration in autumn associated with the percent increase in 25(OH)D concentration [coefficient −0.28 (SE0.12), $P = 0.02$]. There was no association between the percent change in $1,25(OH)_2D$ and the percent change in 25(OH)D. However, the percent increase in $1,25(OH)_2D$ was inversely associated with the percent increase in plasma creatinine [coefficient −0.63 (SE0.18), $P = 0.001$]. In women, the percent decrease in DPD/Cr in autumn was negatively associated with the percent increase in 25(OH)D [coefficient −0.82 (SE0.36), $P = 0.03$] but not with the percent decrease in PTH.

4 Discussion

This study observed significant seasonal changes in some biochemical markers of bone metabolism and bone mineral measurements at the hip in an older northern Chinese population. The biological significance of the seasonal changes had yet to be determined. However, it is clear that these seasonal variations have to be considered when interpreting the results of laboratory or bone mineral measurements in cross-seasonal studies in

this population.

Serum calcium and phosphate concentrations have been suggested to be affected by season by some studies[5,16]. In the present study, plasma calcium and phosphate concentrations were higher in autumn compared with spring. However, plasma 25(OH)D but not 1,25 $(OH)_2D$ concentration was increased in autumn. Therefore, the increased plasma calcium and phosphate concentrations could not be explained by 1,25$(OH)_2D$. This is interesting and is in line with recent studies suggesting that 25(OH)D may promote calcium absorption in its own way[22]. Higher urinary calcium excretion or Ca/Cr in autumn compared with spring has also been reported[5,23]. Though not significant, an average of 11% increase in urinary Ca/Cr in autumn was observed in our study (Table 1).

The decrease in DPD/Cr in autumn coincided with the increase in 25(OH)D but not with the decease in PTH in women in this study. Lack of associations between plasma concentrations of PTH and biochemical markers of bone turnover or bone mineral status has been observed in this population before[19]. The reason for this is not clear but we are currently conducting a detailed study to investigate the metabolic effect of PTH on bone turnover in this population. In agreement with another study investigating seasonal variations in bone markers[5] we did not find significant seasonal change in the bone formation marker, osteocalcin.

We observed an inverse association between the change in plasma creatinine and 1,25 $(OH)_2D$. An inverse association between serum creatinine and 1,25 $(OH)_2D$ was also reported in a cross-sectional study in elderly[24]. In our study the mean plasma creatinine concentration in women was higher in autumn suggesting the renal function of some women was deteriorated. This could explain in part the absence of seasonal increase in plasma 1,25 $(OH)_2D$ concentration in autumn in the women.

Despite 6 month older in age, significant increases in femoral neck BMC and total hip BMD were found in women in autumn. An increase in total hip BMD was also seen in men. Significant seasonal variations in BMD or BMC have been observed by some[12-15,25] but not other researchers[9-11,16,17]. The relative increases in BMC or BMD in autumn compared with spring do not suggest these subjects do not lose bone with age and this has been demonstrated nicely by a study in elderly women. In this study, significant seasonal variations in BMD at the trochanter was observed but overall BMD at the site decreased about 3% over 2 years[26].

Gender difference in seasonal change in some biochemical markers was observed. Firstly, the bone resorption marker urinary DPD/Cr in autumn was decreased 50% in women but no decrease was seen in men. Secondly, men had a greater increase in plasma 25(OH)D concentration in autumn compared with women, and 1,25 $(OH)_2D$ concentration was also increased whereas no increase in 1,25 $(OH)_2D$ was observed in women. Gender differences in bone mineral and skeletal remodelling indexes have been reported before[5,7] suggesting the seasonal variations in bone metabolism are more pronounced in women.

In summary, this longitudinal study in an older northern Chinese population demonstrates significant seasonal changes in some biochemical markers of bone metabolism and bone mineral status at the hip, especially in women. Further investigations with larger sample numbers are needed to examine seasonal effects on bone mineral status at other skeletal sites and perhaps other biochemical markers of bone turnover.

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