

## **Vitamin D status and bone turnover markers among Han-Chinese men**

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### **Abstract**

This work aims to investigate the changing characteristics of calcium-regulating hormones and bone turnover markers (BTMs) among Han-Chinese men in a Beijing community. A retrospective analysis was carried out by studying the general information and the data of calcium-regulating hormones (25-hydroxyvitamin D [25(OH)D], parathyroid hormone [PTH]) and bone turnover markers (procollagen type 1 amino-terminal propeptide [P1NP], osteocalcin [OC] and C-terminal cross-linking telopeptide [CTX]) from 2792 Han-Chinese men, who were selected from those attending routine physical examinations in a Beijing community. The effect of vitamin D status on the bone turnover markers was investigated. For the sample population (aged 24 to 97 years), serum concentrations of 25(OH)D were found to be  $19.84 \pm 8.65$  ng/ml. The serum PTH concentration showed a tendency to increase with age and was negatively associated with serum calcium concentrations ( $r = -0.3192$ ,  $P < 0.0001$ ). The levels of P1NP were found to decrease with age ( $P < 0.01$ ), so was the level of CTX ( $P < 0.01$ ). The level of OC reached a maximum at 40-49 years of age, and then declined with age ( $P < 0.01$ ). It was shown that the bone turnover markers were negatively associated with 25(OH)D: OC ( $r = -0.1690$ ,  $P < 0.0001$ ), P1NP ( $r = -0.1799$ ,  $P < 0.0001$ ) and CTX ( $r = -0.1822$ ,  $P < 0.0001$ ). Among the Han-Chinese men, the bone turnover markers increased with age, and were negatively associated with 25(OH)D.

**Keywords:** Han-Chinese men, 25-hydroxyvitamin D, bone turnover markers

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### **Introduction**

Bone tissue undergoes a constant metabolic turnover involving osteoclasts leading to bone resorption and osteoblasts for the compensatory phase of bone formation. Under physiological conditions there is a balance between the two. However, when an imbalance occurs due to a preponderance of resorption, bone mass loss occurs, leading to osteoporosis (OP), a skeletal disease characterized by low bone mass and micro architectural deterioration of the bone tissue that results in an increase in bone fragility and susceptibility to fracture. Although osteoporosis is more common in postmenopausal women, it is also a significant health issue for the male population.

About one-third of hip fractures occur in men worldwide. Men have two to three times the mortality rate of women as a result of hip fractures. According to the epidemiological data in China, the prevalence of osteoporosis is estimated to be 5.5% - 15.5% for men and 11.8 - 24.5% for postmenopausal women. According to an estimate by WHO, in the next 50 years, about 50% of hip fracture

incidence will be in Asia. Osteoporosis in men has now been recognized as an increasingly important public health issue in China, the most populous developing country.

Although the measurement of bone mineral density (BMD) remains a fundamental method for osteoporosis diagnosis and fracture risk prediction, a number of biochemical bone turnover markers (BTMs) can reflect the osteoclast and osteoblast activities and bone metabolism process, also provide valuable information for the rate of bone loss and the related fracture risk, as well as osteoporosis treatment monitoring.

Biochemical bone turnover markers (BTMs) are the metabolites produced in the process of bone remodeling (or bone metabolism), which are divided into bone formation markers and bone resorption markers. The former includes bone alkaline phosphatase (BALP), osteocalcin (OC), procollagen carboxy-terminal propeptide (PICP), procollagen type 1 amino-terminal propeptide (P1NP), etc., reflecting osteoblast activities and bone formation;

the latter includes tartrate-resistant acid phosphatase (TRACP), N-terminal type I collagen telopeptide (NTX), C-terminal type I collagen telopeptide (CTX), pyridinoline (PYD), deoxypyridinoline (DPYD), etc., representing the metabolites of osteoclast activities and bone resorption, especially bone matrix degradation products. Recent studies have recommended using P1NP and CTX-I as the bone turnover markers [1]. According to the clinical practice guideline on osteoporosis in men [2], biochemical bone turnover markers (markers of bone formation such as P1NP and markers of bone resorption such as CTX or NTX) should be monitored every 3-6 months before and after treatment with anti-osteoporosis drugs. But there are fewer studies for men on the changing characteristics of bone turnover status based on large-sample investigations.

Vitamin D is an important hormone for skeletal health, and serum 25-hydroxyvitamin D [25(OH)D] is the barometer for vitamin D status in the body. Based on the current general classification of vitamin D status [3], 25(OH)D > 30ng/ml: vitamin D sufficient; between 20-30ng/ml: vitamin D insufficient; 25(OH)D < 20ng/ml: vitamin D deficient. Vitamin D insufficiency or deficiency is highly prevalent worldwide. It is believed that with adequate Vitamin D status, serum 25(OH)D should reach 30ng/ml or above for efficacious PTH suppression [4]. Lower serum 25(OH)D concentrations (10 - 20 ng/ml), reduced intestinal absorption of calcium, secondary hyperparathyroidism, increased bone turnover, and eventually result in bone loss and increased fracture risk. Moreover, lower 25(OH)D levels can lead to the occurrence of osteomalacia.

At present, most studies have focused on bone turnover status for postmenopausal women [5, 6], while there are fewer studies for men on the changing characteristics of bone turnover status based on large-sample investigations. And there are relatively fewer studies on the effect of vitamin D status on the bone turnover markers in men. In this study, a retrospective analysis was carried out, based on the data collected from a total of 2792 Han-Chinese men from a Beijing community. The study includes the effect of age on the variations in serum concentrations of biochemical BTMs, the vitamin D status, as well as their correlations.

## Material and Methods

### Patients

The study population comprised a sample of 2845 Han-Chinese men in a Beijing community, who were selected from those attending routine physical examinations in 2012. This study was conducted in accordance with the declaration of Helsinki and with approval from the Ethics Committee of Chinese PLA General Hospital. Written informed consent was obtained from all participants. Pa-

tients were excluded if: 1) they had severe liver or kidney disease; 2) they had metabolic bone disorders due to complications of other diseases, such as primary or secondary hypogonadism, hyperparathyroidism, hyperthyroidism, chronic obstructive pulmonary disease, etc.; 3) they were taking or had taken certain drugs that may affect bone metabolism, including steroid hormone, gonadotropin releasing hormone analogue, etc.; 4) they had a medical history of bone tumor; 5) they had taken osteoporosis medications (e.g., bisphosphonates, calcitonin, strontium ranelate, triparatide, etc.); 6) they were heavy drinkers or smokers; 7) they were recently bed-ridden for over three months. In total, 2792 eligible participants were included in the study.

### Sample collection and measurement

Fasting serum samples were collected from all participants and measured using electrochemiluminescence immunoassays (E170, Roche Diagnostics, Basel, Switzerland) for the levels of calcium, phosphorus, total alkaline phosphatase (AP), 25(OH)D, parathyroid hormone (PTH), P1NP, OC and the bone resorption marker CTX. In addition, the serum samples were also used to assess renal and liver functions. All sample collections were completed in May 2012.

### Statistical analysis

Statistical analysis was performed using SPSS 19.0 (IBM Corporation, Armonk, New York). The data were presented as the mean  $\pm$  standard deviation (SD). The comparisons among the groups were analyzed by chi-square test, and pair-wise comparisons were performed using LSD test. All data were expressed in percentage terms. Linear correlation analysis was also carried out using Pearson correlation, followed by stepwise multiple logistic regression analysis. In all the comparisons, the p-value for statistical significance was defined as  $P < 0.05$ .

## Results

### Comparisons of general characteristics

Table 1 listed the general characteristic data for the 2792 men included in the study, who were aged 24 to 97 years. As shown in Table 1, the heights, weights and body mass indices (BMI) of the patients tended to increase with age (the mean value of  $P < 0.001$ ), while the serum creatinine levels increased with age ( $P < 0.001$ ). The liver function tests for all the participants were within normal limits.

### Vitamin D, serum calcium and PTH

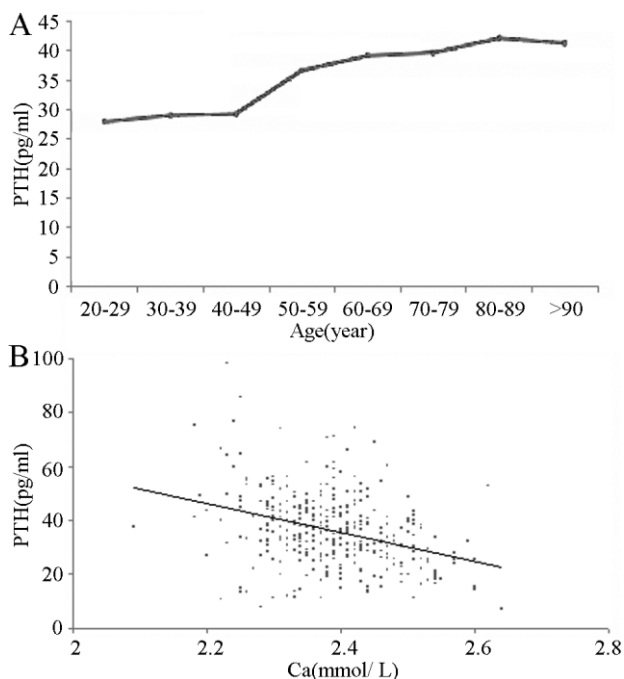
The serum 25(OH)D levels for the study group were in the range of  $19.84 \pm 8.65$  (4.00-81.98)ng/ml. Among the 2792 participants, 334 were vitamin D sufficient (>30ng/ml), accounted for 11.96%; 818 were insufficient (20-30ng/ml), accounted for 29.30%; 1640 were deficient (<20ng/ml), accounted for 58.74%. This was based on the

nutritional status classification [3].

The levels of serum calcium were found to decrease with age, while the serum PTH concentrations showed a tendency to increase with age with more significant changes after the age of 50 (see Figure 1A). In addition, there was a negative correlation between serum PTH and serum calcium concentrations ( $r=-0.3192$ ,  $P < 0.0001$ ), as shown in Figure 1B.

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A7°
20-29 30-39 40-49 50-59 60-69 70-79 80-89 90
Age(year)
24
20-29 30-39 40-49 50-59 60-69 70-79 80-89 90
Age(year)
C 0.50
0.20
0.15
0.10
0.05
20-29 30-39 40-49 50-59 60-69 70-79 80-89 90
Age(year)
    
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**Figure 1.** Effect of age on serum PTH, and the correlation between serum PTH and serum calcium concentrations. The serum PTH (Figure 1A) concentrations showed a tendency to increase with age with more significant changes after the age of 50. In addition, there was a negative correlation (Figure 1B) between serum PTH and serum calcium concentrations ( $r=-0.3192$ ,  $P < 0.0001$ ).

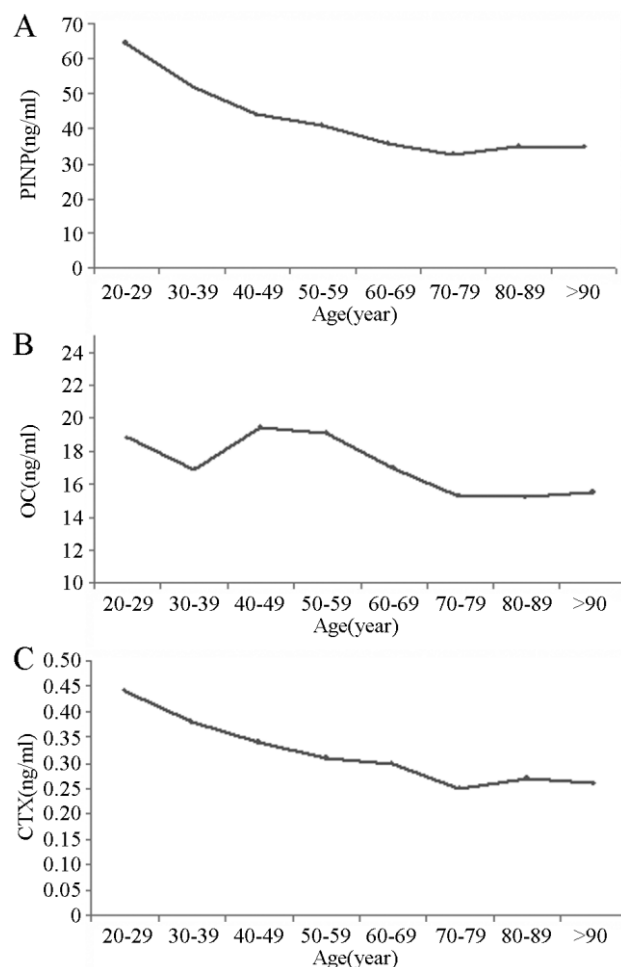
**Age effect**

As shown in Figure 2A, the levels of serum P1NP were found to decrease with age ( $P < 0.01$ ), while the levels of OC reached a maximum at 40-49 years of age (see Figure 2B), and then decreased with an increase in age ( $P < 0.01$ ). The levels of CTX were also found to decrease with age ( $P < 0.01$ ), as shown in Figure 2C. However, all these three indicators showed no significant changes after the age of 70 ( $P > 0.05$ ).

**25OHD effect**

The participants were divided into four groups based on their vitamin D status (Vd): Vd<10 ng/ml, Vd=10~20 ng/ml, Vd=20~30 ng/ml and Vd >30 ng/ml. Comparisons were made among different groups on the levels of serum PTH and BTMs. As shown in Table. 2, there were no significant differences in the levels of serum PTH, while the serum concentrations of P1NP, OC and CTX showed a decreasing trend ( $P < 0.001$ ) with increasing 25(OH)D levels.

Pearson regression analysis showed that the levels of 25(OH)D were negatively correlated with levels of the BTMs: OC ( $r=-0.1690$ ,  $P < 0.0001$ ); P1NP ( $r=-0.1799$ ,  $P < 0.0001$ ); CTX ( $r=-0.1822$ ,  $P < 0.0001$ ).



**Figure 2:** Effect of age on the BTMs. The levels of serum PINP (Figure 2A) were found to decrease with age ( $P < 0.01$ ), while the levels of OC (Figure 2B) reached a maximum at 40-49 years of age, and then declined with age

( $P < 0.01$ ). The levels of CTX (Figure 2C) were also found to decrease with age ( $P < 0.01$ ). However, all these three indicators showed no significant changes after the age of 70 ( $P > 0.05$ ).

**Table 1.** Comparisons of general characteristic data among different age groups

Index	Total (Mean±Std)	20-29ys	30-39ys	40-49ys	50-59ys	60-69ys	70-79ys	80-89ys	>90 ys	P-value
No. of cases (N)	2792	113	398	257	344	515	481	605	79	-
Height (cm)	169.5±7.1	174.92±6.01	172.66±5.67	170.81±5.10	173.02±6.09	172.39±5.56	169.71±5.13	167.94±5.64	164.14±7.13	<.0001
Weight (Kg)	71.5±11.5	77.34±9.95	76.22±10.26	75.58±9.57	77.52±9.71	74.97±9.23	70.64±9.00	68.72±10.30	63.30±11.15	<.0001
BMI (kg/m <sup>2</sup> )	24.77±3.10	25.32±3.45	25.54±3.03	25.88±2.86	25.87±2.58	25.20±2.65	24.51±2.79	24.30±3.14	23.41±3.21	<.0001
Creatinine (umol/L)	80.90±17.43	83.87±9.06	82.06±10.19	82.05±10.09	82.12±11.99	81.53±12.62	84.08±16.29	89.74±21.93	95.91±25.57	<.0001
ALT (U/L)	20.53±12.53	27.18±16.95	23.53±11.76	24.36±12.40	23.16±12.69	21.37±11.19	19.89±12.09	17.51±9.68	13.67±6.00	<.0001
AST (U/L)	21.21±8.78	20.88±6.75	20.03±6.13	20.61±6.34	21.41±6.47	21.98±6.65	22.05±7.50	22.50±13.73	20.85±6.75	<.0001
Calcium (mmol/L)	2.39±0.10	2.47±0.09	2.47±0.09	2.41±0.09	2.37±0.08	2.36±0.08	2.36±0.09	2.36±0.10	2.36±0.10	<.0001
Phosphorus (mmol/L)	1.12±0.15	1.19±0.15	1.15±0.16	1.11±0.15	1.14±0.15	1.09±0.15	1.06±0.14	1.09±0.13	1.13±0.15	<.0001
PTH (pg/ml)	37.10±15.94	28.05±9.76	29.06±9.53	29.30±11.71	36.67±15.23	39.21±14.17	39.66±15.09	42.21±17.32	41.34±19.95	<.0001
VD (ng/ml)	19.84±8.65	16.88±5.05	15.18±4.53	15.03±5.23	18.37±6.79	21.97±8.22	22.73±9.45	22.01±10.22	21.36±10.62	<.0001
PICP (ng/ml)	40.03±21.17	64.63±23.49	52.28±26.01	43.76±13.84	40.94±17.35	35.82±14.68	32.74±21.84	35.00±18.93	34.51±13.16	<.0001
OC (ng/ml)	16.92±7.87	18.82±4.85	16.91±5.22	19.45±10.08	19.09±10.43	16.99±7.36	15.32±6.38	15.22±6.71	15.54±6.40	<.0001
CTX (ng/ml)	0.31±0.16	0.44±0.14	0.38±0.14	0.34±0.13	0.31±0.13	0.30±0.17	0.25±0.14	0.27±0.17	0.26±0.16	<.0001

**Table 2.** Effect of 25(OH)D on the bone turnover markers

category	Vd<10	10≥Vd<20	20≥Vd<30	Vd≥30	P
N	220	1420	818	334	
PTH (pg/ml)	39.27±17.67	37.05±16.63	36.82±13.14	34.71±12.69	0.0526
OC (ng/ml)	18.89±10.56	17.72±8.28	15.50±5.33	14.81±5.77	<.0001
PINP (ng/ml)	42.21±15.76	42.80±23.88	37.46±17.95	32.41±14.60	<.0001
CTX (ng/ml)	0.35±0.16	0.33±0.16	0.29±0.15	0.25±0.15	<.0001

## Discussion

Many studies have shown that a high bone turnover rate indicates an increased osteoporotic fracture risk for postmenopausal women [6]. Both the OFELY (Os des Femmes de Lyon) and the EPIDOS (Epidemiologie de l'Ostéoporose) studies confirmed that increased levels of bone resorption markers such as CTX in women, may double their fracture risks, and their effects are independent of BMD measurements.

In similar studies in men (e.g. MINOS [7] and MrOS [8]), however, no correlation was found between the levels of bone resorption markers and osteoporotic fracture. Kanazawa *et al.* [9] showed that the ratio of OC / BALP was an independent predictor of vertebral fracture in Japanese men with diabetes. A study in Finland [10] indicated that an elevated risk of fracture was associated with a lower ratio of carboxylated to total serum osteocalcin. The Dubbo Osteoporosis Epidemiological Study [11] suggested that elevated bone resorption markers of serum C terminal

telopeptide, (ICTP) was an independent risk factor of Osteoporotic fracture for older men.

Regarding the effect of age on the BTMs, it has been reported that slightly elevated levels of BTMs were found in men over 60, which were also associated with the decrease of BMD [12].

The Shanghai osteoporosis study (SOS) [13] investigated the effect of age on bone turnover markers by studying 649 healthy Han-Chinese men (aged 20-89) who were long-term residents in Shanghai, and the results showed that PINP and CTX were negatively correlated with age. Zhao *et al.* [14] observed 389 cases of 20 to 80-year-old healthy men about the effect of age on the serum levels of BALP, OC and NTX. The results showed that the highest levels were found in the 20 to 29 age group, and subsequently decreased with increasing age, reaching the lowest levels at 50 to 59 years old. The results also showed that all three indicators were negatively correlated with

BMD.

This study demonstrated that, among the Han-Chinese men (aged 24 to 97 years), the level of bone formation marker P1NP decreased with age so did the level of bone resorption marker CTX. The levels of OC reached a maximum at 40-49 years of age, and then decreased with increasing age. However, all these three indicators showed no significant changes after the age of 70.

Most studies for men have confirmed that the levels of BTMs decreased with age, which is different from the case of postmenopausal women. In addition to a natural fluctuation of gonadal hormones with age, which is different for men and women, BTMs can also be influenced by other factors such as heredity, lifestyle, disease and drug effects. For example, common genetic polymorphisms in the NF-kappaB signaling pathway are associated with CTX-I in elderly men [15]; Resistance exercises (REX) significantly increase the level of bone formation markers BALP and OC in men [16]; there are also significant increases in the level of bone turnover marker BALP and CTX for men with hyperthyroidism [17]. In addition, for young men on a short-term low-calcium diet with a large intake of carbonated beverages, there will be significant increases in serum concentrations of phosphate, 1,25(OH)<sub>2</sub>D, PTH, OC, CTX and NTX, without any marked changes in their serum calcium levels [18]. Recently it has been reported in numerous studies that the level of 25(OH)D in men was negatively correlated with BTMs [13, 19].

Vitamin D is an important hormone for skeletal health. According to a study for Beijing in the 1980s (samples collected in July), the level of serum 25(OH)D for an average adult was in the range of  $18.9 \pm 6.5$  ng/ml. In 2009, a cross-sectional study with 50-70 years old in Beijing and Shanghai (1,443 men and 1,819 women) showed that serum 25(OH)D levels below 20ng/ml accounted for 69.2%, with 93.6% lower than 30ng/ml.

The Shanghai osteoporosis study (SOS) [13] tested winter samples from 649 healthy Han-Chinese men (aged 20-89) who were long-term residents in Shanghai, and serum 25(OH)D was measured in the range of 22.8 (19.1-27.0) ng/ml, with 84.0% lower than 20ng/ml.

This study showed that, among Han-Chinese men in a Beijing community (aged 24-97, samples collected in May), vitamin D levels were in the range of  $19.84 \pm 8.65$  ng / ml, with 11.96% being vitamin D sufficient (> 30ng/ml), 29.30% being vitamin D insufficient (20-30ng /ml) and 58.74% being vitamin D deficient (<20 ng/ml).

Although vitamin D insufficiency is highly prevalent worldwide, there are also racial, national, and regional

differences. For example, higher levels of vitamin D were observed in Lhasa ( $27.6 \pm 14.1$  ng/ml) [20] and Guangdong province ( $27.93 \pm 13.94$  ng / ml) [21] in China, which are higher than in Beijing area. In addition, vitamin D level may also be affected by factors of sun exposure, dietary intake and personal lifestyles.

There are disagreements with respect to the effect of vitamin D level on the BTMs in postmenopausal women, with some reports showing no correlations between them. The Pk-VF study [6] in China did not establish the correlation between 25OHD level and BMD or bone fracture, its data, however, indicated that vitamin D status was negatively correlated with the bone turnover markers (P1NP and CTX). Kunchuk *et al* [22] made similar observations.

There are relatively fewer reports on vitamin D status and bone turnover markers in men. The European Male Aging Study (EMAS) [23] analyzed 2783 men (aged 40-79) to investigate the effect of vitamin D on BTMs and BMD, the results suggested that 25(OH)D level was negatively correlated with PTH, and positively correlated with BMD, but not correlated with the BTMs PICP and CTX. The results in this study showed that 25(OH)D level was negatively correlated with the BTMs P1NP, OC and CTX, which was consistent with two other research studies in China [13, 19].

The possible mechanisms of the effect of vitamin D include PTH signaling pathways. Although some studies suggested that the correlation between 25(OH)D and OC are independent of PTH, there is overwhelming evidence [24, 25] for vitamin D deficiency-induced secondary hyperparathyroidism, increased levels of bone turnover markers, falls and osteoporotic fractures. However, this study could not confirm the negative correlation between 25(OH)D and PTH.

## Conclusion

In this research, we studied a sample of Han-Chinese men from a Beijing community to investigate the variation in levels of calcium-regulating hormones and the biochemical bone turnover markers. The results showed that the biochemical bone turnover markers increased with age, and were negatively associated with 25(OH)D. The exact mechanism, however, still needs further research. Although based on a large-sample size, this was a cross-sectional study and did not take into account other factors, such as dietary calcium intakes, sun exposure and personal lifestyles, etc. Therefore, the results of this study should not be generalized to other male populations. Also, further investigations are required to elucidate the correlations of calcium-regulating hormones and bone turnover markers with osteoporosis and osteoporotic fractures.

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