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Original Article

Correlation of serum uric acid with bone mineral density and fragility fracture in patients with primary osteoporosis: a single-center retrospective study of 253 cases

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Abstract: Objective: This study aimed to investigate the correlation of serum uric acid with bone mineral density (BMD) and fragility fracture in primary osteoporosis (PO) patients. Methods: A retrospective analysis of biochemical parameters including bone turnover markers and bone density was done in patients (n=253) received initial treatment for PO from January 2011 to May 2012 at the Shanghai First People's Hospital. Results: Pearson correlation analysis and multiple regression analysis showed that serum uric acid positively correlated with the lumbar spine BMD ($P<0.05$); serum uric acid negatively correlated with urine calcium/creatinine ratio, but positively correlated with blood 25-hydroxyvitamin D (25 [OH] D) ($P<0.05$); the serum uric acid in postmenopausal women with the history of fragility fracture was significantly lower than that in women without the this disease history. Conclusion: Serum uric acid may be a protective factor of bone metabolism in primary osteoporosis patients.

Keywords: Osteoporosis, fractures, bone density, uric acid

Introduction

Hyperuricemia is one of risk factors of metabolic syndromes, renal diseases, and cardiovascular diseases [1-4]. However, studies show that uric acid plays an important role in the oxidative stress [5, 6], and oxidative stress has been found to be an important factor in the pathogenesis of bone loss due to primary osteoporosis [7]. Thus, there might be a reduction in serum uric acid which is also associated with the bone loss. At present, few studies have been conducted to investigate the relationship between serum uric acid and bone loss. This study was undertaken to retrospectively investigate the correlation of serum uric acid with the bone mineral density (BMD) and fragility fracture in patients with primary osteoporosis.

Patients and methods

Patients

A total of 253 patients who received initial treatment for primary osteoporosis from January 2011 to May 2012 in the Shanghai First People's Hospital were retrospectively reviewed. There were 32 males with an average age of 65.690 ± 10.081 years and 221 females with an average age of 67.310 ± 11.792 years. All these patients were diagnosed with primary osteoporosis and the liver and kidney function was normal. Exclusion criteria: secondary osteoporosis; diseases affecting the bone metabolism (such as cancer, rheumatoid arthritis, thyroid diseases, chronic persistent liver diseases, and kidney diseases); use of active vitamin D or other anti-osteoporosis drugs, or treatment with non-active vitamin D of >800 U/d within past six months, or use of these drugs for more than six months; the presence of treatments which can inhibit uric acid synthesis or treatment with uricosuric drugs; estrogen (androgen) replacement therapy, steroid therapy and therapy with drugs affecting bone metabolism within past six months.

Methods

Biochemical tests: Biochemical markers of bone metabolism: detection of serum 25-hydro-

Table 1. Basic clinical data

	Patients (n=253)	Q1 (n=141)	Q2 (n=112)	*P* value
Serum uric acid (mmol/L) (x ± s)	295.4 ± 76.7	<300	≥300	0.000
Age (yr) (x ± s)	65.9 ± 10.3	65.6 ± 10.3	66.3 ± 10.4	0.620
BMI (kg/cm^2) (x ± s)	23.46 ± 3.77	22.71 ± 3.74	24.39 ± 3.60	<0.001*
History of fragility fracture [n (%)]	77 (30.40)	46	31	0.376
History of hypertension [n (%)]	3 (0.60)	2	1	0.711
History of diabetes mellitus [n (%)]	22 (4.40)	11	11	0.544
History of coronary heart disease [n (%)]	6 (1.20)	2	4	0.255
History of cerebrovascular accident [n(%)]	24 (4.80)	15	9	0.508
Ca (mmol/L) (x ± s)	2.26 ± 0.10	2.26 ± 0.10	2.26 ± 0.10	0.279
P (mmol/L) (x ± s)	1.21 ± 0.15	1.21 ± 0.16	1.21 ± 0.14	0.800
BGP (mmol/L) (x ± s)	18.47 ± 6.76	19.35 ± 7.15	17.33 ± 6.07	0.019*
β-CTX (x ± s)	485.55 ± 464.85	531.40 ± 586.11	426.67 ± 218.73	0.078
uCa/Cr (x ± s)	0.42 ± 0.25	0.43 ± 0.23	0.41 ± 0.28	0.481
25(OH)D (x ± s)	49.33 ± 17.48	47.84 ± 15.14	51.82 ± 20.27	0.078
Cholesterol (x ± s)	5.19 ± 0.92			
Triglyceride (x ± s)	1.49 ± 0.79	1.35 ± 0.60	1.65 ± 0.95	0.005*
BMD (g/cm^2) (x ± s)				
L1-4	0.944 ± 0.186	0.909 ± 0.186	0.989 ± 0.175	0.001*
Neck of femur	1.275 ± 1.041	1.394 ± 1.034	1.124 ± 1.033	0.041*
Hip	0.813 ± 0.153	0.795 ± 0.151	0.837 ± 0.153	0.029*

Footnotes: *P<0.05.

Table 2. Correlation analysis of BMD and uric acid after adjusting age and gender

BMD (g/cm^2)	*B*	SE	*P*
L1-4	526.763	186.068	0.005*
Femoral neck	7.784	4.628	0.094
Hip	84.297	77.614	0.278

Footnotes: *P<0.05.

Table 3. Correlation of BMD and indicators of bone biochemics after adjusting age and gender

	B	SE	Beta	*P*
Ca	84.943	51.749	0.109	0.102
P	3.448	35.963	0.007	0.924
BGP	-0.958	0.809	-0.084	0.238
β-CTX	-0.010	0.011	-0.059	0.384
UCa/Cr	-59.375	20.354	-0.193	0.004*
25 (OH) D	0.615	0.283	0.139	0.031*

Footnotes: *P<0.05.

xyvitamin D (25-HD): fasting blood was collected at 8:00-10:00 and stored at -80°C for use. Electrochemiluminescence (Germany Roche E170) was employed to detect the serum 25-HD.

Bone mineral density (BMD): The dual-energy x-ray absorptiometry (Lunar, Prodigy; USA) was used to measure the BMD of lumbar spine (L) and left femoral neck (Neck). Phantom test was performed before each measurement. The L, 4CV was 1.5%, the whole hip CV was 1.2% and the femoral neck CV was 1.7%. BMD was conducted by the same technician.

Statistical analysis

SPSS version 17.0 software was used for statistical analysis. Data with normal distribution were expressed as means ± standard deviation (x ± s) and compared with t test; data with abnormal distribution were expressed as medians and converted into data with normal distribution for statistical analysis. Pearson linear correlation analysis was used for the analysis of correlation; stepwise regression was employed to evaluate the influence of different factors on the BMD at different sites. Logistic regression analysis was used to identify the independent factors influencing the BMD.

Table 4. Logistic regression analysis of independent factors of fragility fracture

Factors	x^2	df	*P*
BMD of hip	27.961	1	0.000
Urinary calcium (UCa)	34.584	2	0.000
Osteoporosis with coronary heart disease (CAD)	38.937	3	0.000
Blood phosphorus (P)	42.857	4	0.000
Vitamin D (Vit D)	47.456	5	0.000

Results

General information

A total of 253 patients were recruited of who 221 were females and 32 were males. The mean age was 65.9 ± 10.3 years, and the body mass index (BMI) was 23.45 ± 3.76 kg/cm^2. The concomitant diseases included hypertension, diabetes mellitus coronary heart disease and cerebrovascular accidents (**Table 1**). In addition, fragility fracture was found in 77 patients (30.4%). Of these patients, vertebral fracture was found in 49 patients, hip fracture in 15 and fracture at other sites (ribs, wrist, ankle and shoulder) in 25. Of note, 11 patients developed fractures at multiple sites. According to serum uric acid, patients were classified into Q1 group (serum uric acid of <300 μmol/L) and Q2 group (≥300 μmol/L). No significant difference was found in the age between two groups (*P*=0.620). However, the BMI in Q2 group was significantly higher than that in Q1 group (*P*<0.001), the serum osteocalcin in Q1 group was markedly higher than that in Q2 group (*P*=0.019), the triglyceride in Q2 group was significantly higher than that in Q1 group (*P*=0.005), and the BMD of L1-4, femoral neck and hip in Q1 group was markedly lower than that in Q2 group (*P*<0.05).

Correlation of serum uric acid and BMD and biochemical markers of bone metabolism

After adjusting confounding factors such as age and gender, multiple regression analysis was used to evaluate the correlation of serum uric acid with BMD and biochemical markers of bone metabolism. Results showed that the BMD of lumbar spine highly correlated with the serum uric acid (*P*=0.005), but the BMD of hip was not associated with the serum uric acid (*P*=0.278). In addition, the serum uric acid was closely related to the urinary calcium/creatinine ratio and serum 25 (OH) D (*P*=0.004, and *P*= 0.031, respectively) (**Tables 2** and **3**).

Multivariate analysis of the impact fracture

In the stepwise regression analysis, fracture served as a dependent variable, and age, gender, BMI, serum uric acid, bone metabolism markers and comorbidities as independent variables. Results showed that the hip BMD, urinary calcium/creatinine ratio, phosphorus, 25 (OH) D and coronary heart disease and cerebrovascular accidents were independent risk factors of fracture (**Table 4**).

Discussion

Serum uric acid is an important antioxidant *in vivo*. Our results showed that the serum uric acid was positively related to the BMD of lumbar spine, suggesting that a high blood uric acid may be helpful to prevent osteoporosis. Gout patients are usually complicated by bone and joint diseases, and recently, *in vitro* studies have shown that uric acid crystals can inhibit the generation of osteoblasts and osteoclasts, which supports the above hypothesis. Therefore, for patients with osteoporosis, it is necessary to dynamically monitor the blood uric acid, and to control the blood uric acid within normal range may be beneficial to improve the BMD. Many clinical studies have confirmed that oxidative stress is a detrimental factor for bone metabolism, and a major cause of bone loss. Thus, uric acid may act to improve BMD and reduce osteoporosis via its strong anti-oxidative effects. Wang et al. [8] also showed that the serum uric acid was associated with the BMD of lumbar spine, femoral neck and trochanter. Zhuang et al [9] performed the ultrasonography of right calcaneus in the old outpatients with hyperlipidemia, and results showed the bone strength in these patients was significantly lower than that in patients without hyperlipidemia, regardless of gender. Above findings were consistent with our findings that serum uric acid is closely associated with BMD.

The correlation between serum uric acid and bone metabolism may be explained by other

possible metabolic factors (such as calcium and PTH) that may affect the uric acid clearance [10, 11]. Studies have found that serum uric acid is positively related to PTH, suggesting that PTH may play an important role in the relationship between serum uric acid and bone metabolism. Our results showed that the serum uric acid was no associated with PTH, but closely related to the urinary calcium/creatinine. In the multivariate analysis of fragility fracture, results showed the urinary calcium was an independent factor affecting the fragility fracture. This suggests that urinary calcium is an important mediator between serum uric acid and bone metabolism. Dong et al proposed that the increased serum uric acid could promote the recovery of fracture via its antioxidative effects [11]. Our results showed serum uric acid was not an independent risk factors of fragility fracture, but whether to raise the serum uric acid is helpful to improve the BMD and promote the fracture recovery is required to be further studied. In contrast, there is evidence showing that blood phosphorus and vitamin D are independent factors affecting the occurrence of fracture. Particularly in osteoporosis patients with a history of coronary heart diseases or cardiovascular and cerebrovascular accidents, both are risk factors of fragility fractures, and should be emphasized in clinical practice.

Uric acid may not only benefit the bone metabolism (anti-oxidative effect), but be deleterious for it (uric acid crystals induced bone destruction) [12]. Therefore, for osteoporosis patients, to control the serum uric acid in a level slightly higher than the upper limit of normal will help to improve BMD, but it is necessary to confirm the range of serum uric acid in which the bone metabolism is not influenced. Thus, more in-depth studies with large sample size are required to elucidate it.

Disclosure of conflict of interest

None.

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