CLINICAL ARTICLE

Higher concentration of serum C-terminal cross-linking telopeptide of type I collagen is positively related with inflammatory factors in postmenopausal women with H-type hypertension and osteoporosis

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Objective: To investigate the changes of inflammatory factors and bone metabolism markers in postmenopausal women with H-type hypertension and to assess the relationship between them.

Methods: Postmenopausal women who were diagnosed with osteoporosis were selected as observation objects. Participants were divided into three groups: only osteoporosis group (osteoporosis group), hypertension combined with osteoporosis group (hypertension group), and H-type hypertension combined with osteoporosis group (H-type hypertension group). The changes in bone mineral density and bone metabolic markers (osteocalcin [OC], procollagen type I N-terminal propeptide (PINP), and C-terminal cross-linking telopeptide of type I collagen [CTX]) and inflammatory factors (interleukin-6 [IL-6] and tumor necrosis factor-α [TNF-α]) were compared among three groups.

Results: In the hypertension group and the H-type hypertension group, the bone mineral density of the lumbar spine (0.647 ± 0.038 *vs* 0.638 ± 0.034 *vs* 0.668 ± 0.047, $P < 0.05$) and the femoral neck (0.567 ± 0.047 *vs* 0.552 ± 0.053 *vs* 0.618 ± 0.059, $P < 0.05$) was significantly lower than that in the osteoporosis group. The concentrations of CTX (266.61 ± 64.65 *vs* 293.09 ± 72.34 *vs* 235.48 ± 62.85, $P < 0.05$), IL-6 (44.36 ± 6.45 *vs* 48.05 ± 8.04 *vs* 39.06 ± 7.95, $P < 0.05$) and TNF-α (30.53 ± 6.28 *vs* 34.52 ± 7.15 *vs* 28.66 ± 6.19, $P < 0.01$) in the hypertension group and in the H-type hypertension group were significantly higher than those in the osteoporosis group. The concentrations of OC (30.59 ± 6.43 *vs* 27.10 ± 6.51, $P < 0.05$) and PINP (36.36 ± 6.16 *vs* 33.16 ± 6.77, $P < 0.05$) in the H-type hypertension group were increased dramatically. The concentration of CTX was positively correlated with the concentration of IL-6 ($r = 0.587$, $P < 0.01$) and TNF-α ($r = 0.474$, $P < 0.01$) and negatively related with the concentration of OC ($r = -0.591$, $P < 0.01$) and PINP ($r = -0.646$, $P < 0.01$) and the bone mineral density of the lumbar spine ($r = -0.470$, $P < 0.01$) and the femoral neck ($r = -0.509$, $P < 0.01$).

Conclusion: Higher concentration of serum CTX is found in postmenopausal women with H-type hypertension, which is positively correlated with inflammatory factors. Besides, H-type hypertension could further enhance the activity of osteoclasts and increase the expressions of inflammatory factors, resulting in the aggravation of osteoporosis.

Key words: C-terminal cross-linking telopeptide of type I collagen; H-type hypertension; Osteoporosis; Inflammatory factors; Bone mineral density

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Grant Sources: This study was supported by the young medical talents project of Jiangsu Province of China (grant no. QNRC2016382).
Disclosure: The authors declared no potential conflicts of interest.
Received 31 July 2018; accepted 8 October 2019

Introduction

People with H-type hypertension are more likely to have osteoporosis. With the growth in the aging population, more and more people are suffering from this type of disease. Patients with primary hypertension and hyper homocysteine (HCY) are hereby designated as having H-type hypertension. It had been shown by Valentina Fratoniv that increased blood homocysteine could lead to decreasing bone mass and osteoporosis[1]. The results of Unay K showed that hypertension was a high-risk factor for primary osteoporosis[2]. Therefore, as patients with H-type hypertension have two high-risk factors at the same time, they deserve particular attention[3]. Although studies on H-type hypertension and osteoporosis have been published, the mechanism between them remains unclear[4,5]. In patients with H-type hypertension, the expressions of inflammatory factors are substantially increased, while in patients with osteoporosis, the level of osteoclasts is increased. However, the relationship between activity of osteoclasts and serum inflammatory factors in postmenopausal women with H-type hypertension has not been evaluated.

Osteoporosis patients have no apparent clinical symptoms in the early stage, but in the later stage, they are liable to fracture, so quality of life is severely affected[6]. Bone metabolism is a dynamic equilibrium process involving bone formation and bone absorption[7]. Once the balance of the body is broken, osteoclasts are more active than osteoblasts, which can lead to osteoporosis[8,9].

Bone metabolism markers can reflect the state of bone transformation in the body, with high sensitivity and specificity, and have important clinical significance in the study of the pathogenesis of osteoporosis and the efficacy of drugs[10]. Interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α) are not only critical inflammatory factors in the body but also among the elements that promote bone absorption and cause bone formation disorders[11,12].

The purpose of our study was to evaluate: (i) changes in bone metabolic markers and inflammatory factors in postmenopausal women with H-type hypertension and osteoporosis; (ii) the correlation between serum CTX and bone metabolic markers, bone mineral density, and inflammatory factors in postmenopausal women with H-type hypertension and osteoporosis; and (iii) anti-osteoporosis treatment to improve the quality of patients.

Materials and Methods

Clinical Data

A total of 266 postmenopausal women who were diagnosed with osteoporosis in the Third Affiliated Hospital of Soochow University from January 2014 to June 2018 were the subjects of the present study. Before patients were included in this study, they had discontinued β-receptor blockers, angiotensin converting enzyme inhibitors or angiotensin II receptor antagonist, diuretics, and other antihypertensive drugs for more than 2 weeks, and discontinued aldosterone receptor antagonist for 3 weeks. People who cannot stop taking anti-hypertensive drugs may choose to use α-receptor blocker. Written informed consent was given by all participants. In our study, the protocol was approved by The Research and Ethics Committees of the third affiliated hospital of Soochow University, which included permission for additional measurements in stored serum samples.

According to the World Health Organization's diagnostic criteria of primary osteoporosis, dual energy X-ray absorptiometry was used to measure bone mineral density. We diagnosed osteoporosis when the bone mineral density of the T-Score was less than −2.5 SD. Even if the blood pressure of the participant who had a history of hypertension was lower than 140/90 mmHg when she was taking antihypertensive drugs, she was still diagnosed as having hypertension. Participants with primary hypertension accompanied by hyper homocysteine were known as having H-type hypertension. Participants with secondary hypertension, parathyroid disease, severe liver and kidney disease and various malignancies, and participants who had been on bone metabolism drugs were excluded. Participants were divided into three groups: an only osteoporosis group (osteoporosis group), a hypertension combined with osteoporosis group (hypertension group), and an H-type hypertension combined with osteoporosis group (H-type hypertension group). There were 92 participants in the osteoporosis group, 88 participants in the hypertension group, and 86 participants in the H-type hypertension group.

Baseline Data

The average age was measured and body mass index (BMI) was calculated as body weight/height^2 (kg/m^2). For biochemical analyses, all blood samples were collected in the morning after at least 10 h of fasting. The samples were promptly centrifuged. Supernatants were separated. The concentrations of fasting plasma glucose (FPG), total cholesterol (TC), and triglyceride (TG) were measured using the enzymatic colorimetric method.

Bone Mineral Density

Bone mineral density T-Scores were used to identify participants with osteopenia or osteoporosis based upon World Health Organization criteria[13]. Using dual energy X-ray absorptiometry (HOLOGIC Discover, USA), we measured the bone mineral density of the lumbar spine and the femoral neck (g/cm^2); T-Scores were obtained for each participant. Osteopenia was defined as bone mineral density T-Score from −1 to −2.5, and osteoporosis was defined as T-Score below −2.5. The quality assurance for dual energy X-ray absorptiometry was performed every morning using standards provided by the manufacturer.

Bone Metabolic Markers

C-terminal cross-linking telopeptide of type I collagen (CTX) is a small peptide fragment released after type-I collagen degradation. It is a specific marker of bone absorption. In the

clinic, we evaluate bone resorption in patients with osteoporosis by detecting the serum level of CTX. Osteocalcin (OC) is a nonspecific collagen, mainly produced by osteoblasts. It enters into circulation when the bone matrix breaks down. Therefore, detection of OC in the blood can reflect the activity of osteoblasts. Procollagen type I N-terminal propeptide (PINP) is released during the process of type-I collagen synthesis and reflects the changes in type-I collagen. It is a sensitive and specific indicator for the activity of osteoblasts. In the clinic, we evaluate bone synthesis by detecting the serum levels of PINP and OC. After at least 10 h of fasting, all blood samples were collected. Serum was separated by centrifugation and was stored at −20°C. Bone metabolic markers, such as OC, PINP, and CTX, were measured using Roche Elecsys 2010 type automatic electrochemical luminescence immunity analyzer and accessory kits.

Serum Inflammatory Factors and Homocysteine

Inflammatory markers can affect the differentiation, proliferation, and apoptosis of osteoblasts and osteoclasts by autocrine and paracrine, thus regulating bone reconstruction. IL-6 and TNF-α are the most relevant inflammatory markers in elderly patients with hypertension and osteoporosis. Hyper homocysteine (HCY) combined with primary hypertension is known as H-type hypertension. Elevated homocysteine in the body can cause bone loss and osteoporosis. Therefore, there are extremely close relationships between them. Blood samples were collected in the morning after ten hours of fasting. Serum was promptly centrifuged. The concentrations of IL-6, TNF-α, and HCY in serum were measured by enzyme-linked immunoassay using reagents from R&D Systems.

Statistical Analysis

SPSS 18.0 (SPSS, USA) is used to tackle all statistical analyses. Quantitative variables were presented as mean ± standard deviation. The Kolmogorov–Smirnov test was used to determine the distribution characteristics of variables, and Levene's test was used to determine the equality of variance. Differences in multiple groups were analyzed by one-way ANOVA with least significance difference multiple comparison post hoc. Associations between continuous variables were evaluated using a univariate linear regression test.

TABLE 2 Comparison of bone mineral density among three groups

Groups	*n*	Lumbar spine (g/cm^2)	Femoral neck (g/cm^2)
Osteoporosis	92	0.668 ± 0.047	0.618 ± 0.059
Hypertension	88	0.647 ± 0.038 [a]	0.567 ± 0.047 [b]
H-type hypertension	86	0.638 ± 0.034 [b]	0.552 ± 0.053 [b]
F-test		13.282	37.245
P-value		0.000	0.000

Comparison with osteoporosis group, [a]$P < 0.05$, [b]$P < 0.01$; comparison with hypertension group, [c]$P < 0.05$, [d]$P < 0.01$.

The Spearman correlation test was used to evaluate the associations between serum CTX level and serum cytokine levels. Two-tailed *P*-values < 0.05 were considered statistically significant. All figures were performed using SPSS.

Results

Baseline Data

In total, 266 postmenopausal women who were diagnosed with osteoporosis were recruited in our study. The patients of three groups were matched in average age and BMI. The baseline biochemical results, such as for age, BMI, fasting plasma glucose (FPG), total cholesterol (TC) and triglyceride (TG) levels, are shown in Table 1. There are no statistical differences among the three groups ($P > 0.05$). Besides, no significant correlations were observed between CTX and age, BMI, FPG, TC, and TG levels in patients with H-type hypertension and osteoporosis (Table 1).

Bone Mineral Density

In comparison with the osteoporosis group, the bone mineral density of the lumbar spine (0.668 ± 0.047 *vs* 0.647 ± 0.038 *vs* 0.638 ± 0.034, $P < 0.05$) and the femoral neck (0.618 ± 0.059 *vs* 0.567 ± 0.047 *vs* 0.552 ± 0.053, $P < 0.01$) was significantly lower in the hypertension group and the H-type hypertension group, and differences were statistically significant (Table 2).

TABLE 1 Comparison of baseline data among three groups (mean ± SD)

Groups	*n*	Age (years)	BMI (kg/m^2)	FPG (mmol/L)	TC (mmol/L)	TG (mmol/L)
Osteoporosis	92	62.48 ± 4.83	25.83 ± 6.78	6.22 ± 0.23	4.76 ± 0.58	1.46 ± 0.36
Hypertension	88	61.97 ± 4.68	26.43 ± 5.31	1.58 ± 0.29	6.41 ± 0.39	4.97 ± 0.42
H-type hypertension	86	62.09 ± 4.06	26.18 ± 4.87	6.36 ± 0.58	4.65 ± 0.74	1.68 ± 0.45
F-test		0.645	1.831	0.347	0.856	0.936
P-value		0.587	0.249	0.427	0.387	0.687

BMI, body mass index; FPG, fasting plasma glucose; TC, total cholesterol; TG, triglycerides. Comparing with osteoporosis group.

TABLE 3 Comparison of bone metabolism markers among three groups

Group	*n*	CTX (ng/mL)	OC (ng/mL)	PINP (ng/mL)
Osteoporosis	92	235.48 ± 62.85	27.10 ± 6.51	33.16 ± 6.77
Hypertension	88	266.61 ± 64.65 [a]	29.29 ± 7.30	35.54 ± 6.38
H-type hypertension	86	293.09 ± 72.34 [bc]	30.59 ± 6.43 [a]	36.36 ± 6.16 [a]
F-test		16.684	6.089	5.952
P-value		0.000	0.003	0.003

CTX, C-terminal crosslinking telopeptide of type I collagen; OC, osteocalcin; PINP, procollagen type I N-terminal propeptide.; Comparison with osteoporosis group, [a]$P < 0.05$, [b]$P < 0.01$; comparison with hypertension group, [c]$P < 0.05$, [d] $P < 0.01$.

Bone Metabolic Markers

Compared with the osteoporosis group, CTX in the hypertension group and the H-type hypertension group (235.48 ± 62.85 *vs* 266.61 ± 64.65 *vs* 293.09 ± 72.34, $P < 0.05$) increased significantly, and differences were statistically significant. Compared with the osteoporosis group, the concentrations of OC (27.10 ± 6.51 *vs* 29.29 ± 7.30, $P > 0.05$) and PINP (33.16 ± 6.77 *vs* 35.54 ± 6.38, $P > 0.05$) in the hypertension group increased, but there were no statistical differences. The levels of OC (27.10 ± 6.51 *vs* 30.59 ± 6.43, $P < 0.05$) and PINP (33.16 ± 6.77 *vs* 36.36 ± 6.16, $P < 0.05$) in the H-type hypertension group increased significantly, and differences were statistically significant (Table 3).

Serum Inflammatory Factors and Homocysteine

Compared with the osteoporosis group, the concentration of IL-6 in the hypertension group and the H-type hypertension group (39.06 ± 7.95 *vs* 44.36 ± 6.45 *vs* 48.05 ± 8.04, $P < 0.05$) increased significantly. In comparison with the hypertension group, the concentration of IL-6 (44.36 ± 6.45 *vs* 48.05 ± 8.04, $P < 0.05$) was also increased in the H-type hypertension group, and differences were statistically significant. Levels of TNF-α (34.52 ± 7.15 *vs* 30.53 ± 6.28, $P < 0.05$) and Homocysteine (17.19 ± 4.57 *vs* 15.49 ± 4.65, $P < 0.05$) in the H-type hypertension group were higher than those in the hypertension group, and the differences were statistically significant (Table 4).

TABLE 4 Comparison of inflammatory factors and homocysteine among three groups

Group	*n*	IL-6 (pg/mL)	TNF-α (pg/mL) homocysteine (μmol/L)
Osteoporosis	92	39.06 ± 7.95	28.66 ± 6.19 14.76 ± 4.41
Hypertension	88	44.36 ± 6.45[a]	30.53 ± 6.28 15.49 ± 4.65
H-type hypertension	86	48.05 ± 8.04[bd]	34.52 ± 7.15[bc] 17.19 ± 4.57[bc]
F-test		32.187	18.494 6.710
P-value		0.000	0.000 0.001

IL-6, interleukin -6; TNF-α, tumor necrosis factor-α; comparison with osteoporosis group, [a]$P < 0.05$, [b]$P < 0.01$; comparison with hypertension group, [c]$P < 0.05$, [d]$P < 0.01$.

Relationship between Serum CTX and Serum Cytokine Levels

To assess the potential relationships between the concentration of CTX and the levels of inflammatory factors, homocysteine, and bone metabolism markers in patients with H-type hypertension combined with osteoporosis, the correlations between CTX and IL-6, TNF-α, HCY, OC, and PINP were analyzed using Spearman's correlation test. The results indicated that the concentration of serum CTX was positively correlated with the level of serum IL-6 (Fig. 1A, $r = 0.587$, $P = 0.000$) and TNF-α (Fig. 1B, $r = 0.474$, $P = 0.000$). However, the concentration of CTX was negatively correlated with the level of serum OC (Fig. 1C, $r = -0.591$, $P = 0.001$) and PINP (Fig. 1D, $r = -0.646$, $P = 0.000$). There was no correlation between the concentration of CTX and HCY (Fig. 1E, $r = 0.001$, $P = 0.995$).

Relationship between Serum CTX and Bone Mineral Density

The correlations between CTX and the bone mineral density of the lumbar spine and the femoral neck were analyzed using Spearman's correlation test. The results indicated that the concentration of serum CTX level was negatively correlated with the bone mineral density of the lumbar spine (Fig. 2A, $r = -0.470$, $P = 0.000$) and the femoral neck (Fig. 2B, $r = -0.509$, $P = 0.000$).

Discussion

Osteoporosis is a kind of metabolic disease characterized by low bone mass, bone tissue microstructure damage, and bone brittleness increase[14]. The advantages of dual energy X-ray absorptiometry are high accuracy, stability, and low radiation dose[15]. However, it cannot detect osteoporosis in the early stages. In additino, it only reflects the amount of bone mineral and does not reflect changes in bone

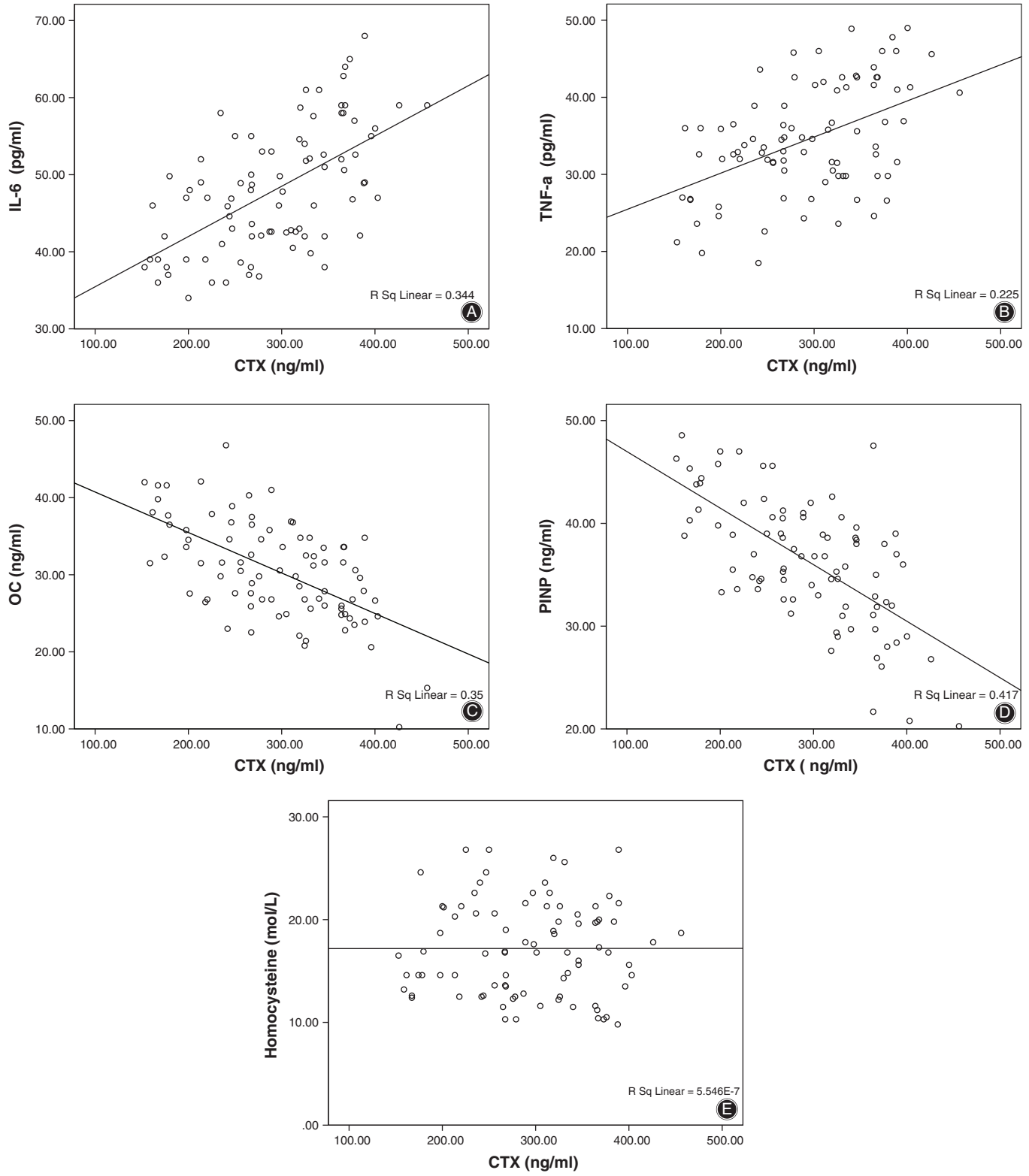

Fig. 1 The relationship between serum C-terminal cross-linking telopeptide of type I collagen (CTX) and cytokine among three groups: (A) the concentration of serum CTX was positively correlated with the level of interleukin-6 (IL-6); (B) the concentration of CTX was positively correlated with TNF-α; (C) the concentration of CTX was negatively correlated with the level of OC; and (D) the concentration of CTX was negatively correlated with the procollagen type I N-terminal propeptide (PINP). E, There was no correlation between the concentration of CTX and HCY.

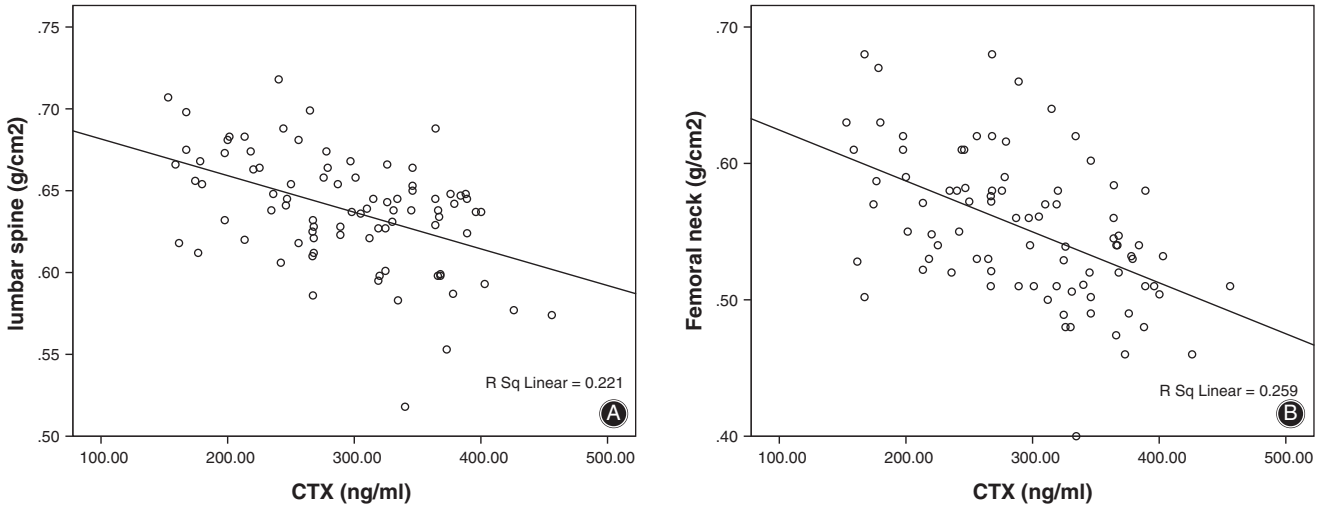

Fig. 2 The relationship between serum C-terminal cross-linking telopeptide of type I collagen (CTX) and bone mineral density among three groups. (A) The concentration of CTX was negatively correlated with the bone mineral density of the lumbar spine; and (B) the concentration of CTX was negatively correlated with the bone mineral density of femoral neck.

metabolism. Bone metabolism markers can reflect changes in bone metabolism and bone reconstruction in the short term, which is closely related to the balance of bone loss and bone synthesis[16,17]. Therefore, early detection of changes in bone metabolism markers is conducive to the selection of appropriate therapeutic drugs and drug efficacy evaluation[18].

Studies on the correlation between hypertension and osteoporosis have been reported. The bone mineral density of the femoral neck in postmenopausal women with hypertension over 56 years old is significantly lower than that in the non-hypertension group. Such results had been described in the study by Yang *et al.*[19]. Patients with both primary hypertension and hyper homocysteine are known as having H-type hypertension[20]. Enneman *et al.* found that elevated homocysteine in the body can cause bone loss and osteoporosis[21]. Our research indicates that bone mineral density of the lumbar spine and the femoral neck in H-type hypertension combined with the osteoporotic group are significantly lower than those in the osteoporosis group. Once osteoporosis patients suffer from H-type hypertension, the level of bone density decreases rapidly. Therefore, there are extremely close relationships between them.

The results of Van Ballegooijen *et al.* showed that there was an apparent abnormal bone metabolism existed in hypertensive patients[22]. Usually, 90% of bone organic matter composition in a human body is composed of type-I collagen, and the type-I collagen is degraded very little. However, in the pathological condition, the activity of osteoclast has significantly been enhanced, and a large amount of type-I collagen is degraded. CTX is a small peptide fragment released after type-I collagen degradation, which has no cross-reaction with other collagen. It is a specific marker of bone absorption[23]. In the present study we found that the level of CTX in H-type the hypertension group was significantly higher than that in the osteoporosis group. It indicated that in patients with H-type hypertension, the activity of osteoclasts was increased dramatically; the ability of bone resorption was also enhanced remarkably. Therefore, in the clinic, we could evaluate bone resorption in patients with osteoporosis by detecting the serum level of CTX.

Osteocalcin is a nonspecific collagen, mainly produced by osteoblasts. It enters into circulation when the bone matrix breaks down. Therefore, detection of OC in the blood may well reflect the activity of osteoblasts[24]. PINP is released during the process of type-I collagen synthesis, and reflects the changes in type-I collagen. When the synthesis of osteoblasts increases, the level of PINP rises. It is a sensitive and specific indicator for the activity of osteoblasts[25,26]. The results of our study showed that the concentrations of OC and PINP in the H-type hypertension group were improved compared with those in the osteoporosis group. Therefore, in patients with osteoporosis, H-type hypertension can lead to the activity of osteoblasts increasing. These results were consistent with those of Kalaiselvi[27]. In the clinic, we could evaluate bone synthesis in patients with osteoporosis by detecting the serum levels of PINP and OC.

By improving the expression of endothelial cytokines, hypertension and blood pressure variation stimulate inflammation to cause target organ damage[28]. Blood pressure variation is associated with vascular damage and inflammatory markers such as IL-6 and TNF-α. IL-6 is the most relevant indicator in elderly patients with hypertension and osteoporosis. Inflammatory markers can affect the differentiation, proliferation, and apoptosis of osteoblasts and osteoclasts by autocrine and paracrine, thus regulating bone reconstruction[29]. In our study, the levels of IL-6 and TNF-α in the

H-type hypertension group were significantly higher than those in the osteoporosis group. The differences are statistically significant. This indicates that in H-type hypertension, the levels of inflammatory factors are increased, which destroys the balance between osteoblasts and osteoclasts and causes the increase in bone absorption and the deterioration of osteoporosis. Therefore, clinically, by detecting the levels of serum inflammatory factors such as IL-6 or TNF-α, we could further assess the state of bone metabolism in patients with osteoporosis.

There were some limitations in our study. First, the number of participants in our study was insufficient; however, this can be enlarged in future study. Second, inflammatory factors detected in our study were IL-6 and TNF-α. Other novel inflammatory factors can be detected in future experiments. Third, blood pressure was recorded in this study. In future, blood pressure should be recorded.

In conclusion, after menopause, estrogen levels in the female are decreasing, while bone absorption and bone formation are accelerating. The process of bone conversion is very rapid. In postmenopausal women with H-type hypertension, not only the activity of osteoclasts and the level of CTX are increased, but also the activity of osteoblasts is increased. Inflammatory factors are also increased. However, the concentration of serum CTX level is positively correlated with inflammatory factors. Therefore, in postmenopausal women with H-type hypertension, the process of bone absorption is significantly higher than bone formation, resulting in further deterioration of osteoporosis. In the clinic, it is critical to detect the bone metabolism markers and inflammatory factors as early as possible.

Acknowledgments

All authors thank the participants, medical staff, and nurses.

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